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VOLUME 7

1920-1921

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CONTENTS

The following papers have been published during the years 1920-1921. Papers marked with an asterisk (*) are not included in this volume.

Adair, F. L., and Scammon, R. E. 1. A study of the ossification centers of the wrist, knee and ankle at birth, with particular reference to the physical development and maturity of the newborn. *American Journal of Obstetrics and Gynecology,* 2:3-28 (1921).

Barry, L. W. *1. The effects of inanition on the pregnant albino rat, with especial reference to the changes in the relative weights of the various parts, systems, and organs of the offspring. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-sixth session. *Anatomical Record,* 18:221 (1920).
*2. The effects of inanition in the pregnant albino rat, with special reference to the changes in the relative weights of the various parts, systems, and organs of the offspring. *Contributions to Embryology,* Carnegie Institute of Washington, 53:91-136 (1920).
3. The effects of inanition in the pregnant albino rat, with special reference to the changes in the relative weights of the various parts, systems, and organs of the offspring. *Papers from the Mayo Foundation and the Medical School.* W. B. Saunders Company, Philadelphia and London. 1:590-640 (1921).

Calkins, L. A. *1. The growth of the external dimensions of the human body in the fetal period and its expression by empirical formulae. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:47-48 (1921).

Dunn, H. L. *1. The growth of the brain and the spinal cord in the human fetus and its expression by empirical formulae. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:55 (1921).
2. The growth of the central nervous system in the human fetus as expressed by graphic analysis and empirical formulae. *Journal of Comparative Neurology,* 33:405-491 (1921).

Hoskins, E. R., and Hoskins, M. M. 1. The inter-relation of the thyreoid and hypophysis in the growth and development of frog larvae. *Endocrinology,* 4:1-32 (1920).

Jackson, C. M. 1. Pioneers in embryology. *Journal of the American Medical Association,* 76:497-500 (1921).
*2. The effects of various types of inanition upon growth and development, with special reference to the skeleton. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:68-69 (1921).
*3. *Morris' Human Anatomy.* General editorship and contributor of section on "The Digestive System." 6th revised edition. 1,164 illustrations, 1,507 pages. P. Blakiston's Son and Co., Philadelphia (1921).

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Jackson, C. M., and Stewart, C. A. 1. The effects of inanition in the young upon the ultimate size of the body and of the various organs in the albino rat. *Journal of Experimental Zoology,* 30:97-128 (1920).

Kudo, Tokuyasu. 1. Studies on the effects of thirst. I. Effects of thirst on the weights of the various organs and systems of adult albino rats. *American Journal of Anatomy,* 28:399-430 (1921).
2. Studies on the effects of thirst. II. Effects of thirst upon the growth of the body and of the various organs in young albino rats. *Journal of Experimental Zoology,* 33:435-461 (1921).

Latimer, H. B. *1. The growth of the organs and systems of the single comb White Leghorn chick. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:70-71 (1921).

Myers, J. A., and Myers, F. J. *1. Studies on the mammary gland. VIII. Gross changes in the mammary gland in the female albino rat during the period of involution. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:74 (1921).
2. Studies on the mammary gland. VII. The distribution of the subcutaneous fat and its relation to the developing mammary glands in male and female albino rats from birth to ten weeks of age. *Anatomical Record,* 22:353-362 (1921).

Noback, G. J. *1. The developmental topography of the thymus, with particular reference to the changes at birth and in the neonatal period. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:75 (1921).
2. A contribution to the topographic anatomy of the thymus gland, with particular reference to its changes at birth and in the period of the newborn. *American Journal of Diseases of Children,* 22:120-144 (1921).

Osterud, H. L. *1. The postnatal growth and development of the female reproductive tract in the albino rat. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:75-76 (1921).

Rasmussen, A. T. *1. The hypophysis cerebri of the American marmot *(Marmota monax)* with special reference to changes during hibernation. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-sixth session. *Anatomical Record,* 18:255 (1920).
*2. The so-called hibernating gland. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:78-79 (1921).
3. The hypophysis cerebri of the woodchuck *(Marmota monax)* with special reference to hibernation and inanition. *Endocrinology,* 5:33-66 (1921).
4. On the organization of neuro-anatomy for medical students upon a thorough-going functional basis where only the human brain is used for dissection. *Anatomical Record,* 22:123-139 (1921).

Roberts, F. L. 1. Changes in the mammary gland of the albino rat *(Mus norvegicus albinus)* during the second half of pregnancy. *Papers from the Mayo Foundation and the Medical School.* W. B. Saunders Company, Philadelphia and London. 1:228-255 (1921). 15 figures.

Rogers, Lee. 1. Observations on the developmental anatomy of the temporal bone. *Annals of Otology, Rhinology and Laryngology,* March, pages 1-12 (1921). 8 plates.

Scammon, R. E. *1. Some general characters of the postnatal growth of the various organs in man. (Abstract.) Proceedings of the American Association of Anatomists. Thirty-sixth session. *Anatomical Record,* 18:256-257 (1920).
*2. On the growth in weight of the human body and its various parts and organs in the fetal period and its expression by empirical formulae. (Abstract.) Proceedings of The American Association of Anatomists. Thirty-seventh session. *Anatomical Record,* 21:79 (1921).
3. A note on the relation between the weight of the thyroid and the weight of the thymus in man. *Anatomical Record,* 21:25-27 (1921).
4. A simple tracing apparatus for making topographic reconstructions. *Anatomical Record,* 21:19-24 (1921).
5. On the weight increments of premature infants as compared with those of fetuses of the same gestation age and those of full-term children. *Proceedings of the Society for Experimental Biology and Medicine,* 19:133-136 (1921).
6. Developmental anatomy. *Morris' Human Anatomy,* 6th revised edition. Section I, pages 5-57. P. Blakiston's Son and Co., Philadelphia (1921).

Scammon, R. E., and Doyle, L. O. 1. Observations on the capacity of the stomach in the first ten days of postnatal life. *American Journal of Diseases of Children,* 20:516-538 (1920).

Scammon, R. E., and Rucker, W. H. 1. Changes in the form and dimensions of the chest at birth and in the neonatal period. *American Journal of Diseases of Children,* 21:552-564 (1921).

Siperstein, D. M. 1. The effects of acute and chronic inanition upon the development and structure of the testis in the albino rat. *Anatomical Record,* 20:355-391 (1921).
*2. The effects of acute and chronic inanition upon the development and structure of the testis in the albino rat. *Papers from the Mayo Foundation and the Medical School.* W. B. Saunders Company, Philadelphia and London. 1:192-220 (1921).

A STUDY OF THE OSSIFICATION CENTERS OF THE WRIST, KNEE AND ANKLE AT BIRTH, WITH PARTICULAR REFERENCE TO THE PHYSICAL DEVELOPMENT AND MATURITY OF THE NEWBORN

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By Fred L. Adair, M.D., F.A.C.S., and Richard E. Scammon, Ph.D.
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ALTHOUGH numerous studies have been made of the prenatal and postnatal course of the ossification of the extremities, systematic observations on the occurrence of ossification centers in the joints at birth are limited to the roentgenographic studies of Pozier (1912) and Hasselwander (1909) and certain earlier medicolegal work. Pozier's study, while based on a large series of cases, was confined to an examination of the ossification of the knee joint in the newborn. Hasselwander studied the ankle only. Students of legal medicine who have investigated this problem have generally limited themselves to the study of the inferior femoral epiphysis, although Corrado (1891) and Toldt (1882) studied both the knee and the ankle centers by section at autopsy. Aside from a series of 10 cases examined by Puyhaubert (1913) no systematic study has been made of ossification of the carpus at birth.

The present study was undertaken with the object of determining the condition of the ossification centers of the wrist, knee and ankle in the newborn, their interrelationships, and particularly their relation to the maturity and to the size of the child. Incidentally we have considered the effect of parity and sex upon the condition of these centers at birth.

Our material consisted of 100 newborn children (45 females and 55 males) taken *seriatim* from the service of the senior author in the Maternity Ward of the Swedish Hospital of Minneapolis. Each of these children was weighed and was measured for total length, and radiographs were made of the ankles, knees and wrists of both sides within 48 hours after birth. The menstrual history of each case was also determined with care, and may be regarded as quite reliable since the mothers were all patients of the better class and of considerable intelligence.*

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*We wish to express our appreciation of the liberality and interest of the Superintendent, G. W. Olson, and the Board of the Swedish Hospital for their support of this study and to acknowledge the cooperation of the supervising nurse, Miss Huseby, and of the radiologist, Miss Anna Johnson.

Of the 100 children studied, 45 were females and 55 were males. The average weight of the entire group was 3374 grams. The females ranged from 2185 to 4440 grams in weight, the average being 3367 grams. The males averaged 3380 grams in weight, the minimum being 2080 grams and the maximum 5060 grams. The average length of the females was 50 cm., the minimum 43 cm. and the maximum 54 cm. The average length of the males was 50.5 cm., the minimum 42 cm. and the maximum 55 cm. The average period of gestation, as calculated from the first day of the last menstruation, was 280 days. The minimum was 233 days and the maximum was 312 days. Of these cases two males and two females were frankly premature as evidenced both by the weight and length and by the menstrual history. The body lengths and weights of three of the male infants distinctly indicated postmaturity although the menstrual history did so in one instance only. Of the hundred children, 64 were firstborn. There were no multiple births in the series.

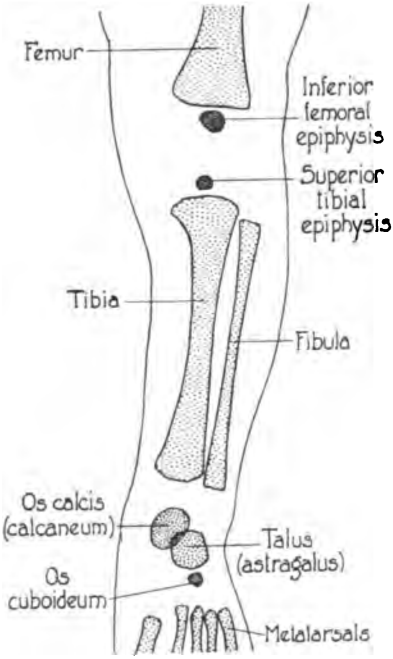

Fig. 1.—Tracing of a radiogram of the right leg of a full-term newborn child showing the various ossific masses. The epiphyses and the os cuboideum are indicated in heavy stipple in this and the following figures of the lower extremity.

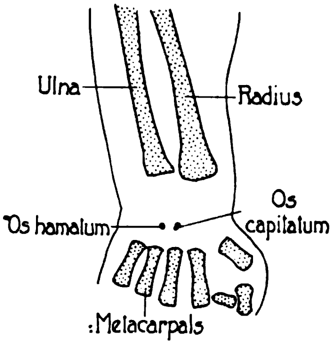

Fig. 2.—Tracing of a radiogram of the right hand of a full-term newborn child showing the various ossific masses.

The ossification centers under consideration will be taken up in the following order; knee, ankle and wrist. Figures 1 and 2 are tracings of radiographs of these regions in the newborn and the various ossific masses which they show have been labeled in accordance with the nomenclature employed in our descriptions.

The Inferior Femoral Epiphysis.—This center was present in 98 per cent of our cases, being absent only twice (in one female and in one male, both of which were frankly premature).

The course of ossification of the inferior extremity of the femur is probably better known than that of any other part of the skeleton. Early in the nineteenth century (1819) Beclard pointed out the significance of this center as a test of the maturity of the newborn. This lead to a series of extended studies of the subject by investigators in legal medicine, among the more important being those of Mildner (1850), Böhm (1858), Pleissner (1861), Casper (1862), Hartmann (1869), Barkow (1872), Toldt (1882), Corrado (1891), Tammasia (1893), and Guichard (1905) all of whom studied the center by section at autopsy. The only extensive radiographic study of the knee of the newborn is that of Pozier (1912) who examined 212 cases. A comprehensive survey of the literature on the subject would probably enable one to bring together records of the development of this center in over 2000 cases in late fetal life and early infancy. From the literature available to us we have collated the records of over 1600 cases and these, together with our series (making a total of 1717 observations), are shown in Table I and are illustrated graphically by the solid line curve in Fig. 26.

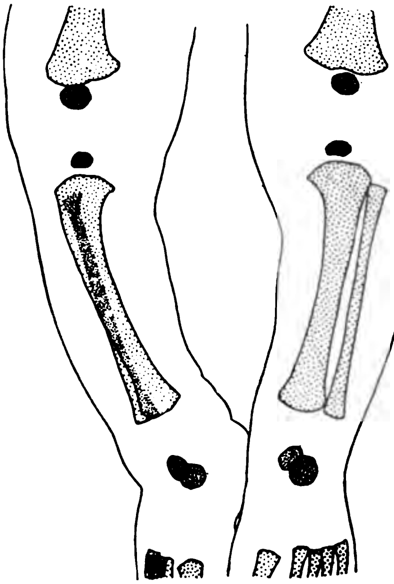

Fig. 3.—Tracing of a radiogram of the lower extremities of a male newborn of 289 days' gestation, having a birth weight of 3350 grams and a total length of 51.5 cm. Large knee centers but no cuboid centers.

TABLE I*

FREQUENCY OF THE OSSIFICATION OF THE INFERIOR FEMORAL EPIPHYSIS IN LATER FETAL LIFE AND IN EARLY INFANCY

AGE	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING A CENTER OF OSSIFICATION	PER CENT OF CASES SHOWING A CENTER OF OSSIFICATION
Seventh fetal month	29	0	0.0
Eighth fetal month	143	7	4.9
Ninth fetal month	181	58	32.0
Tenth fetal month	271	228	84.1
Birth and first week	1004	995	95.1
Second week	42	41	97.6
Third and fourth weeks	70	69	98.6
Second and third months	27	27	100.0

*In tables I, II and III the specimens have been classified on the basis of the original observer's estimate of age or, when this was lacking, on the basis of total body-length interpreted by Hasse's rule.

These data indicate that the appearance of this center prior to seven fetal (lunar) months is extremely exceptional. However, the center may be found in the eighth fetal month, as our data indicate that it is present in approximately 1 case in 20. In the ninth fetal month the frequency of its occurrence rises rapidly, the average for the period being 32 per cent or about 1 case in 3. By the close of the ninth month the center is present in 60 per cent of all cases. This rapid ossification continues through the greater part of the tenth month, the average frequency for this period being 84.1 per cent, or

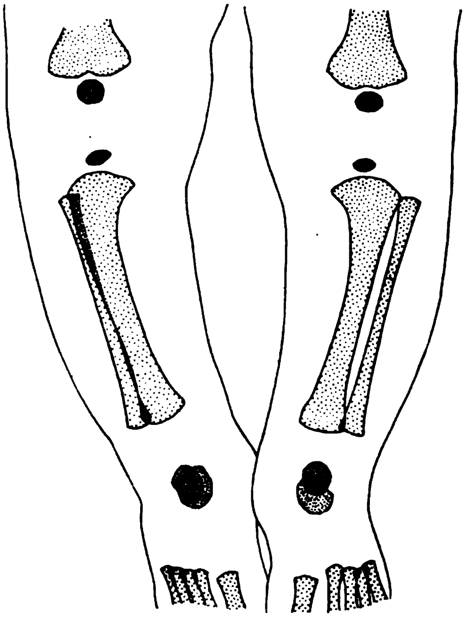

Fig. 4.—Tracing of a radiogram of the lower extremities of a female newborn of 280 days' gestation, having a birth weight of 4440 grams and a total length of 52 cm. Specimen of unusually large dimensions and with large knee centers but no cuboid ossification.

about 6 cases in 7. In the full-term newborn the data indicate that the center is present in about 19 cases in 20. The remaining moiety of the cases ossify rather slowly in the first postnatal month. This may indicate a small group of individuals tending to some perversion of bone development such as fetal rachitis.

On the whole these figures demonstrate that the ossification of the inferior femoral epiphysis is somewhat more precocious than the statements of a number of recent authors would indicate. Since the curve based on the combined data shows that this center is present in fully 50 per cent of all cases in the thirty-sixth week, it is evident that the value of this center as positive evidence of maturity is limited, although as it is usually absent prior to the twenty-eighth week, its presence may be taken as a practically certain indication of viability.

The Superior Tibial Epiphysis.—A definite ossific mass was present in the superior extremity of the tibia in 81 per cent, or slightly more than four-fifths of our series.

TABLE II

FREQUENCY OF THE OSSIFICATION OF THE SUPERIOR TIBIAL EPIPHYSIS IN LATER FETAL LIFE AND AT BIRTH

AGE	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING A CENTER OF OSSIFICATION	PER CENT OF CASES SHOWING A CENTER OF OSSIFICATION
Seventh fetal month	17	0	0.0
Eighth fetal month	34	0	0.0
Ninth fetal month	51	3	5.9
Tenth fetal month	213	88	41.3
Birth	253	195	77.1

The ossification of the superior epiphysis of the tibia has not been the subject of as much investigation as has the inferior femoral. The three main sets of observations on this point of ossification are those of Toldt (1882), Corrado (1891) and Pozier (1912), although Kjölseth (1913) has also reported a few observations. These records, together with our own data (making a total of 568 cases), are summarized in Table II and are shown in graphic form by broken line curve in Fig. 26.

The superior tibial epiphysis appears distinctly later than the inferior femoral. It is apparently always absent in the seventh and eighth months, although one instance of its occurrence in a female fetus of 40 cm. has been reported by Hassenstein (1892). In the ninth month its average frequency for the entire period is approximately 6 per cent, or about 1 case in 17, and according to our graph it is present in about 15 per cent at the end of this time. In the tenth month ossification proceeds very rapidly, the average frequency for the period being slightly above 40 per cent, or about 2 cases in 5. In full-term newborn children this center is present in 75 to 80 per cent of all cases.

Although definite statements regarding the time of appearance of this center are generally lacking even in more recent publications, it is evident from the study of the data presented in the literature and from our own observations that this point of ossification is a better test of maturity than is the inferior femoral epiphysis. The presence of this center indicates in 5 cases out of 6 that the child has passed the ninth fetal month. The lack of this center, however, does not necessarily indicate prematurity as it is absent in nearly a fourth of full-term children at birth.

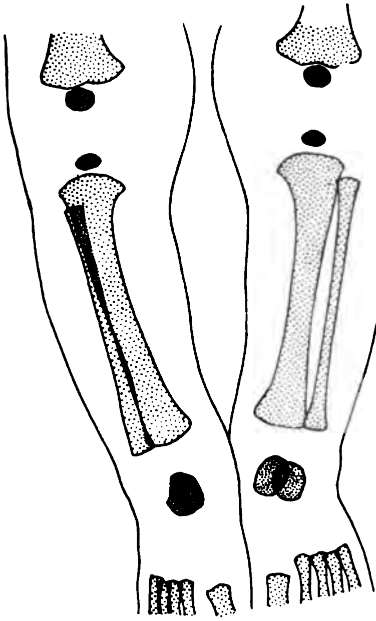

Fig. 5.—Tracing of a radiogram of the lower extremities of a female newborn of 287 days' gestation, having a birth weight of 3390 grams and a total length of 53 cm. Specimen of large dimensions and with large knee centers but no ossification of the cuboid.

TABLE III

FREQUENCY OF THE OSSIFICATION OF THE CUBOID IN LATER FETAL LIFE AND AT BIRTH

AGE	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING A CENTER OF OSSIFICATION	PER CENT OF CASES SHOWING A CENTER OF OSSIFICATION
Seventh fetal month	17	0	0
Eighth fetal month	34	0	0
Ninth fetal month	45	2	4.4
Tenth fetal month	84	23	27.4
Birth	127	77	60.6

THE BONES OF THE ANKLE

The Astragulus (*Talus*) *and Calcaneus.*—The calcaneus is the first bone of the ankle to ossify, making its appearance about the fifth fetal month, and the astragulus undergoes ossification soon thereafter. As these bones were present in all of our cases, as well as in all similar cases reported by others, they require no further discussion.

The Cuboid.—The ossification of the os cuboideum was indicated in 38 per cent of the cases of our series.

The development of the cuboid has been studied by Toldt (1832), Corrado (1891), and Hasselwander (1909) who examined an aggregate of 256 cases. Kjölseth (1913) also studied a small series of cases but her results are published in such form that we cannot include them in our tabulations. The summary of all cases, including our series—a total of 356 cases—is given in Table III and is illustrated by the curve in dotted line in Fig. 26.

Ossification begins in the cuboid, as in the superior tibial epiphysis, in the first part of the ninth fetal month, but proceeds more slowly. The average frequency for the month is 4 per cent, or 1 case in 25. At the end of the ninth month it is present in approximately 12 per cent of all cases, or about 1 case in 8. Like the superior tibial, the frequency of the cuboid center of ossification rises very rapidly in the last fetal month, the average for the period being 26 per cent. In the full-term newborn child the center is present in 60 per cent, or three-fifths of all cases. Thus the significance of the ossification of the cuboid as a test of maturity at birth is about the same as that of the superior tibial epiphysis. Its presence indicates a little more definitely that the child has passed the ninth fetal month but since it is not found in 40 per cent of full-term newborn children its absence cannot be regarded as significant of prematurity.

THE OSSIFICATION OF THE WRIST

The wrist is generally described as cartilaginous at the time of birth although no extensive studies have been made on the condition of the carpus in the newborn. Two bones of the carpus may be present at this time, the os capitatum (magnum) and the os hamatum (unciform). The older writers, who depended on autopsy specimens for their information, Rambaut et Renaut (1864), Béclard (1819), Sappey (1889), Debierre (1889) and others, generally described the os capitatum and os hamatum as appearing between the first and third years, although Meckel (quoted by Puyhaubert 1913) found it present at birth. Students employing radiography, on the other hand, usually report these bones as appearing somewhat earlier. Pryor (1908), whose work on the ossification of the hand is perhaps the most careful and extensive study to date, found that the os capitatum and os hamatum appeared between the third and sixth postnatal months in females and between the fifth and tenth postnatal months in males. Hess (1917) states that these centers may be seen only very rarely at the time of birth. Puyhaubert (1913) examined the wrists of 10 newborn children and found that the capitatum and the hamatum were present in 2 cases. He concluded that the usual time of the ossification of the hamatum was during the first year and of the capitatum from the last fetal month to the close of the first year of extrauterine life. We found some evidences of ossification in the wrist in 15 instances of the series of 100. This indicates that Puyhaubert's figures are a little high, probably through chance in working with such a small series. The os capitatum alone was present in 7 instances, or nearly one-half of the cases showing carpal ossification. In most of the instances in which both points of ossification were present the os capitatum was apparently the larger, although this was not always true. In no case did we find the os hamatum alone present. There has been considerable difference of opinion as to which of these centers is the first to appear. Brice (in Quain 1915) and Nomballais (1909) state that the hamatum is the first to appear. Fuginami (1911) and Rotch (1909) recognize no distinction in the time of appearance of the two centers and Pryor (1908) and Puyhaubert (1913), who have done the most recent work on the subject, regard the capitatum as the first to ossify. Our observations indicate that the last view is the correct one, although the difference in the time of the inauguration of ossification in the two bones cannot be very great.

RELATION BETWEEN OSSIFICATION AND BODY-LENGTH

The relation in our material between body-length and ossification is shown in Table IV. In studying this relation the cases were arranged according to total body-length in 4 classes of which the first 3 were each of 4 centimeters range and the last included all cases of 52 cm. or more.

The inferior femoral center was present in one-half of the cases falling between 40 and 44 cm. and in all cases above 44 cm.

The superior tibial center is closely correlated with body-length. It was present in one-quarter of the cases under 44 cm. and in nearly one-half of the cases between 44 and 48 cm. It was found in approximately five-sixths of all cases of 48 cm. and over, which may be regarded as a mature birth-length.

A peculiar and no doubt accidental condition was found in the relation of the ossification of the os cuboideum to the body-length. The center was present in one-half of the 4 cases having a length of less than 44 cm. and only 22 per cent of those of 44 to 48 cm. But with this exception it occurs in a progressively higher percentage with increasing body-length. It was present in about two-fifths of all children of 48 cm. and over.

No ossification centers in the carpal bones were seen in children of less than 44 cm. in length. The os capitatum was present in approximately one-tenth of all cases having a body-length between 44 and 52 cm. and in about one-quarter of cases of 52 cm. and over. The os hamatum was present in about 6 per cent of cases between 44 and 52 cm. and in about 1 case in 8 of children of 52 cm. and over.

RELATION OF OSSIFICATION TO BODY WEIGHT

The relation of ossification of the various centers under consideration to the weight of the body is shown in detail in Table V, which is of the same general arrangement as Table IV. The various centers will be considered in the order of their appearance.

The inferior femoral epiphysis was present in all of our series, of both sexes, which had a birth weight of 2500 grams or over. In the group of lightest cases (having a birth-weight of 2000 to 2500 grams) the center was present in 50 per cent of the females and in 75 per cent of the males, or in approximately 67 per cent of all cases of this weight. As 2500 grams is probably to be regarded as a very low limit for the normal weight of full-term infants it is probably safe to say that practically all newborn children who exceed the minimum birth weight of maturity possess the inferior femoral epiphysis.

The superior tibial epiphysis also shows a close relation to body-weight. It was absent in all of the females under 2500 grams in weight, in three-fourths of the males and in five-sixths of the total number of cases in this group. The center was present in 83 per cent of children of 2500 grams and over and in 85 per cent of children of 3000 grams or over. It was constantly present only in our group of heaviest cases (4000 grams or over). Thus this center may be expected in approximately five-sixths of all newborn children of mature birth-weight.

These results may be compared with those of Pozier (1912) who also studied the ossification of the knee centers of the newborn by means of radiography. He found the inferior femoral center present in 72 per cent of cases having a birth-weight between 2000 and 2500 grams but only in children of 4000 grams and above was the center constantly present. The average weight of the newborn in Paris is distinctly less than that which has been noted in Minneapolis (approximately 3.23 kg. as compared with 3.38 kg.). This difference might account for the greater frequency of ossification in the group of lighter children but it offers no explanation for the lower frequency of ossification in children of medium weight. The same condition is true for the superior tibial epiphysis since Pozier found this center present in approximately the same per cent of lighter cases as we did, while it was present in a distinctly lower percentage of children of medium weight (3000 to 4000 grams). In the main the results of Pozier and the present findings agree in that frequency of the center is fairly closely related to body-weight.

The os cuboideum, when regarded without distinction of sex, also shows a close correlation to body-weight. It was present in approximately one-sixth of all cases between 2000 and 2500 grams and is found in a progressively increasing percentage of cases up to the group of greatest body-weight (4000 grams and over) where it is noted in about 3 cases out of 5.

The os capitatum (os magnum) was not found in any cases having a body-weight under 2500 grams. It was present in about one-sixth of all cases between 2500 and 4000 grams showing very little correlation with body-weight within these limits. In the group of cases of 4000 grams and over it was present in three cases out of five,—the same frequency as was observed for the os cuboideum.

The os hamatum showed much the same character in its distribution, although it was less frequent than the os cuboideum or os capitatum. It was present in no cases having a body-weight of less than 2500 grams, in about one case in 20 of the children weighing between 2500 and 4000 grams and in 2 out of 5 of the children of 4000 grams and over.

THE RELATION OF OSSIFICATION TO MENSTRUAL AGE

We have estimated the length of gestation of our cases from the menstrual histories, the period of conception being calculated from the first day of the last menstrual period. The relation between body-weight, body-length and the frequency of the various ossification centers to the duration of pregnancy, as determined by this criterion, is shown in Table VI. In this table we have arranged the material in eight groups of ten day periods of menstrual age.

Roughly three-fourths of our cases fall in Groups V, VI and VII ranging in menstrual age from 270 to 300 days. Within these limits the relation between the average body-weight, average body-length and menstrual age is quite constant as both of these values rise steadily with the increasing menstrual age. The percentage frequency of the various centers of ossification studied also shows a close correlation with menstrual age in these groups. The only instance in which the frequency of ossification did not rise with increasing age was in the case of the os hamatum in Groups VI and VII where the cases in which the center was present were less numerous in the larger group. This is probably a chance variation due to the small number of instances in which this center was present.

If, however, one examines the *entire* series of cases the constancy of the relation of menstrual age to bodily development (length and weight) and skeletal development is much less evident and certain striking exceptions appear. This is true of both the younger and the older groups of children. In Group III (250 to 260 days) the body-weight is greater than in any succeeding group and both the body-

TABLE IV

FREQUENCY OF OSSIFICATION OF THE INFERIOR FEMORAL EPIPHYSIS, SUPERIOR TIBIAL EPIPHYSIS, OS CUBOIDEUM, OS CAPITATUM AND OS HAMATUM IN 100 NEWBORN CHILDREN ARRANGED ACCORDING TO BODY-LENGTH

SEX	BODY-LENGTH (CM)	NUMBER OF CASES	FREQUENCY OF OSSIFICATION OF: INFERIOR FEMORAL EPIPHYSIS		SUPERIOR TIBIAL EPIPHYSIS		OS CUBOIDEUM		OS CAPITATUM (MAGNUM)		OS HAMATUM (UNCIFORM)	
			No.	%	No.	%	No.	%	No.	%	No.	%
Females	40 to 44	2	1	(50)	1	(50)	2	(100)	0	(0)	0	(0)
	44 to 48	5	5	(100)	2	(40)	1	(20)	1	(20)	1	(20)
	48 to 52	27	27	(100)	24	(89)	12	(44)	4	(15)	3	(11)
	52 and over	11	11	(100)	10	(91)	5	(45)	1	(9)	1	(9)
	All females	45	44	(98)	37	(82)	20	(44)	6	(13)	5	(11)
Males	40 to 44	2	1	(50)	0	(0)	0	(0)	0	(0)	0	(0)
	44 to 48	4	4	(100)	2	(50)	1	(25)	1	(25)	0	(0)
	48 to 52	28	28	(100)	23	(82)	8	(29)	1	(4)	0	(0)
	52 and over	21	21	(100)	17	(81)	9	(43)	7	(33)	3	(14)
	All Males	55	54	(98)	42	(76)	18	(33)	9	(16)	3	(6)
Both Sexes	40 to 44	4	2	(50)	1	(25)	2	(50)	0	(0)	0	(0)
	44 to 48	9	9	(100)	4	(44)	2	(22)	2	(22)	1	(1)
	48 to 52	55	55	(100)	47	(85)	20	(36)	5	(9)	3	(6)
	52 and over	32	32	(100)	27	(84)	14	(44)	8	(25)	4	(13)
	All Cases	100	98	(98)	79	(79)	38	(38)	15	(15)	8	(8)

TABLE V

FREQUENCY OF OSSIFICATION OF THE INFERIOR FEMORAL EPIPHYSIS, SUPERIOR TIBIAL EPIPHYSIS, OS CUBOIDEUM, OS CAPITATUM AND OS HAMATUM IN 100 NEWBORN CHILDREN ARRANGED ACCORDING TO BODY-WEIGHT

SEX	BODY WEIGHT (KG)	NUMBER OF CASES	FREQUENCY OF OSSIFICATION OF: INFERIOR FEMORAL EPIPHYSIS		SUPERIOR TIBIAL EPIPHYSIS		OS CUBOIDEUM		OS CAPITATUM (MAGNUM)		OS HAMATUM (UNCIFORM)	
			No.	%	No.	%	No.	%	No.	%	No.	%
Females	2.0 to 2.5	2	1	(50)	0	(0)	1	(50)	0	(0)	0	(0)
	2.5 to 3.0	7	7	(100)	4	(57)	2	(29)	1	(14)	1	(14)
	3.0 to 3.5	21	21	(100)	18	(86)	6	(29)	2	(10)	2	(10)
	3.5 to 4.0	11	11	(100)	11	(100)	9	(82)	1	(9)	1	(9)
	4.0 & over	4	4	(100)	4	(100)	2	(50)	2	(50)	1	(25)
	All females	45	44	(98)	37	(82)	20	(44)	6	(13)	5	(11)
Males	2.0 to 2.5	4	3	(75)	1	(25)	0	(0)	0	(0)	0	(0)
	2.5 to 3.0	4	4	(100)	3	(75)	0	(0)	0	(0)	0	(0)
	3.0 to 3.5	21	21	(100)	17	(81)	7	(33)	7	(33)	0	(0)
	3.5 to 4.0	20	20	(100)	15	(75)	7	(40)	3	(15)	0	(0)
	4.0 & over	6	6	(100)	6	(100)	4	(67)	4	(67)	3	(50)
	All Males	55	54	(98)	42	(76)	18	(33)	14	(25)	3	(6)
Both Sexes	2.0 to 2.5	6	4	(67)	1	(17)	1	(17)	0	(0)	0	(0)
	2.5 to 3.0	11	11	(100)	7	(64)	2	(18)	1	(9)	1	(9)
	3.0 to 3.5	42	42	(100)	35	(83)	13	(31)	9	(21)	2	(5)
	3.5 to 4.0	31	31	(100)	26	(84)	16	(55)	4	(13)	1	(3)
	4.0 & over	10	10	(100)	10	(100)	6	(60)	6	(60)	4	(40)
	All Cases	100	98	(98)	79	(79)	38	(38)	20	(20)	8	(8)

length and the ossification is much further advanced than one might expect from the apparent duration of pregnancy. In Group II while

TABLE VI

FREQUENCY OF OSSIFICATION OF THE INFERIOR FEMORAL EPIPHYSIS, SUPERIOR TIBIAL EPIPHYSIS, OS CUBOIDEUM, OS CAPITATUM AND OS HAMATUM IN 100 NEWBORN CHILDREN ARRANGED ACCORDING TO MENSTRUAL AGE

GROUP NUMBER	NUMBER OF CASES	RANGE OF MENSTRUAL AGE (DAYS)	AVERAGE MENSTRUAL AGE (DAYS)	AVERAGE BODY-WEIGHT (GM.)	AVERAGE TOTAL BODY-LENGTH (CM.)	FREQUENCY OF:									
						INFERIOR FEMORAL EPIPHYSIS		SUPERIOR TIBIAL EPIPHYSIS		CUBOID		OS CAPITATUM		OS HAMATUM	
						NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
I	2	230-240	235	2068	43	1	50	0	0	0	0	0	0	0	0
II	3	240-250	248	2525	45	3	100	3	100	2	67	0	0	0	0
III	4	250-260	256	3708	50.5	4	100	3	75	1	25	1	25	0	0
IV	8	260-270	264	3205	50	8	100	5	63	2	25	1	12	1	12
V	25	270-280	275	3318	49.5	24	96	20	80	5	20	2	8	1	4
VI	35	280-290	284	3476	50.5	34	97	28	80	11	31	5	14	3	9
VII	14	290-300	293	3555	51	14	100	14	100	12	86	3	21	2	7
VIII	7	300 & over	305	3335	51	7	100	6	86	5	71	2	29	2	29

TABLE VII

COMPARATIVE FREQUENCY OF THE OSSIFICATION OF THE SUPERIOR TIBIAL EPIPHYSIS, THE INFERIOR FEMORAL EPIPHYSIS AND THE OS CUBOIDEUM IN MALE AND FEMALE FETUSES AND NEWBORN CHILDREN CLASSIFIED BY TOTAL BODY-LENGTH

BODY-LENGTH (CM.)	INFERIOR FEMORAL EPIPHYSIS				SUPERIOR TIBIAL EPIPHYSIS				OS CUBOIDEUM			
	MALES		FEMALES		MALES		FEMALES		MALES		FEMALES	
	NUMBER OF CASES	FREQUENCY OF OSSIFICATION (PER CENT)	NUMBER OF CASES	FREQUENCY OF OSSIFICATION (PER CENT)	NUMBER OF CASES	FREQUENCY OF OSSIFICATION (PER CENT)	NUMBER OF CASES	FREQUENCY OF OSSIFICATION (PER CENT)	NUMBER OF CASES	FREQUENCY OF OSSIFICATION (PER CENT)	NUMBER OF CASES	FREQUENCY OF OSSIFICATION (PER CENT)
40 to 45	25	16.0	26	30.8	23	0.0	20	10.0	17	0.0	19	10.5
45 to 50	113	78.7	109	92.6	100	37.0	102	53.8	31	12.7	33	33.3
50 to 55	127	96.0	97	98.9	122	83.0	91	85.9	54	33.3	47	53.2
55 and over	13	100.0	2	100.0	13	100.0	1	100.0	5	100.0	—	——

the body-length and body-weight are in keeping with the supposed age the ossification is much in advance of it. On the other hand the body-weight of Group VIII (300 days and over) is distinctly below the average weight in Groups III, VI and VII (250 to 260, 280 to 290 and 290 to 300 days respectively) and corresponds quite closely to that of Group V (270 to 280 days). The body-length corresponds quite closely to that of Groups III, VI and VII. The frequency of the ossification of the superior tibial epiphysis and the os cuboideum is distinctly less than in the preceding (and presumably younger group of cases) although the frequency of the ossification of the bones of the wrist is somewhat greater.

TABLE VIII

COMPARATIVE FREQUENCY OF THE INFERIOR FEMORAL EPIPHYSIS IN MALES AND FEMALES IN LATER FETAL LIFE AND AT BIRTH

BODY-LENGTH	FEMALES			MALES		
	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING CENTER	PER CENT OF CASES SHOWING CENTER	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING CENTER	PER CENT OF CASES SHOWING CENTER
Group A Males—40 to 45 cm. Females—39 to 44 cm.	26	7	25.9	25	4	16.0
Group B Males—45 to 50 cm. Females—44 to 49 cm.	76	67	88.1	113	89	78.7
Group C Males 50 to 55 cm. Females—49 to 54 cm.	124	122	98.4	127	122	96.0
Group D Males—55 cm. and over Females—54 cm. and over	5	5	100	13	13	100

TABLE IX

COMPARATIVE FREQUENCY OF THE SUPERIOR TIBIAL EPIPHYSIS IN MALES AND FEMALES IN LATER FETAL LIFE AND AT BIRTH

BODY-LENGTH	FEMALES			MALES		
	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING CENTER	PER CENT OF CASES SHOWING CENTER	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING CENTER	PER CENT OF CASES SHOWING CENTER
Group A Males—40 to 45 cm. Females—39 to 44 cm.	17	1	6.0	23	0	0.0
Group B Males—45 to 50 cm. Females—44 to 49 cm.	71	33	46.5	100	37	37.0
Group C Males—50 to 55 cm. Females—49 to 54 cm.	125	97	77.6	122	89	83.0
Group D Males—55 cm. and over Females—54 cm. and over	4	4	100.0	13	13	100.0

These discrepancies in body-weight, body-length and in the state of the ossification centers in the outlying groups of children when classified by menstrual age seem to us to indicate the great inaccuracies in determining the age of apparently premature and postmature children from the date of the last menstruation alone. This error is evidently twofold, for we find a group of relatively mature children with an average menstrual age of nearly one lunar month (24 days) less than the general average and a group of relatively immature children with an average menstrual age nearly one lunar month (25 days) above the average of all cases. While undoubtedly, in certain instances, the children of these outlying groups are definitely premature or postmature the majority of cases fall in these groups because of inaccuracies in determining the exact duration of prenatal life from the menstrual data. In Group III in particular menstruation probably occurred after conception had taken place, while in Group VIII a menstrual period may have been missed before conception occurred. This speculation would hold true even if we accept the modern opinion that a pregnancy may begin at any time in the intermenstrual period.

As previously stated, we believe that our records of menstrual history are quite accurate for they were obtained by careful inquiry from intelligent patients in private practice. Certainly they are much more precise than the general type of records secured in large maternities accepting all classes. We feel that our data add further evidence of the frequent unreliability of menstrual age, and another argument against the induction of labor at a predetermined date based on the menstrual history.

TABLE X

COMPARATIVE FREQUENCY OF THE CENTER OF OSSIFICATION OF THE CUBOID IN MALES AND FEMALES IN LATER FETAL LIFE AND AT BIRTH

BODY-LENGTH	FEMALES			MALES		
	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING CENTER	PER CENT OF CASES SHOWING CENTER	TOTAL NUMBER OF CASES	NUMBER OF CASES SHOWING CENTER	PER CENT OF CASES SHOWING CENTER
Group A Males—40 to 45 cm. Females—39 to 44 cm.	12	2	16.7	17	0	0
Group B Males—45 to 50 cm. Females—44 to 49 cm.	33	5	15.1	31	4	13
Group C Males—50 to 55 cm. Females—49 to 54 cm.	77	29	37.7	54	18	33
Group D Males—55 cm. and over Females—54 cm. and over	5	1	20.0	5	5	100

RELATION OF OSSIFICATION TO SEX

It is well known that in postnatal life the development of the skeleton proceeds at a more rapid rate and is completed sooner in females than in males. This has been brought out particularly clearly by Pryor's studies on carpal ossification where it was found that certain of the bones which appear rather late in childhood may be present a year or more earlier in the female than in the male. Apparently no study has been made to determine whether this precosity in development of the female exists in the intrauterine life. We have made an attempt to analyze our material from the standpoint of sex by

TABLE XI

COMPARATIVE FREQUENCY OF THE OSSIFICATION OF THE CENTERS OF THE WRIST, KNEE AND ANKLE IN FIRST-BORN AND LATER CHILDREN AT BIRTH

CENTER	MALES (52)				FEMALES (43)				BOTH SEXES	
	FIRST-BORN (39)		LATER CHILDREN (13)		FIRST-BORN (25)		LATER CHILDREN (18)		FIRST-BORN (64)	LATER CHILDREN (31)
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	PER CENT	PER CENT
Inferior femoral epiphysis	38	97.4	13	100	25	100	18	100	98.4	100
Superior tibial epiphysis	33	84.6	8	61.5	19	76.0	17	94.4	81.2	80.6
Cuboid	11	28.2	4	30.7	12	48.0	7	38.9	35.9	35.5
Os capitatum	4	10.2	4	30.7	5	20.0	1	5.6	14.0	16.1
Os hamatum	2	5.1	0	0	4	16.0	1	5.6	9.4	3.2

TABLE XII

TABLE SHOWING THE RELATIVE PERCENTAGE PRESENCE AND ABSENCE FREQUENCY OF THE OSSIFICATION OF THE SUPERIOR TIBIAL EPIPHYSIS, INFERIOR FEMORAL EPIPHYSIS, OS CUBOIDEUM, OS CAPITATUM, AND OS HAMATUM IN 100 NEWBORN CHILDREN

	OS HAMATUM PRESENT	OS HAMATUM ABSENT	OS CAPITATUM PRESENT	OS CAPITATUM ABSENT	CUBOID PRESENT	CUBOID ABSENT	SUP. TIBIAL EPI. PRESENT	SUP. TIBIAL EPI. ABSENT
Os capitatum present	9	6						
Os capitatum absent	0	85						
Cuboid present	9	29	13	25				
Cuboid absent	0	62	2	60				
Sup. tibial epi. present	9	72	15	66	36	45		
Sup. tibial epi. absent	0	19	0	19	2	17		
Int. femoral epi. present	9	89	15	83	37	61	81	17
Int. femoral epi. absent	0	2	0	2	1	1	0	2

grouping it in tables arranged on the basis of period of gestation as determined from the last menstruation, and on body-length. On the last basis we have also made a combined table including all the data of this kind available to us from the literature.

Due to the sources of error in calculating the length of gestation which have been pointed out in a preceding paragraph the analysis of sex differences in ossification based upon the menstrual age gives inconclusive results and on this basis alone no definite and consistent differences in sex could be determined.

The sexual differences in the frequency of ossification in material arranged according to body-length are shown in Tables VII, VIII, IX and X. Table VII shows that when specimens of the two sexes are arranged in groups of equal body-length the frequency of ossification of the various centers is distinctly greater in the females of all groups under 55 cm. than in males. It should be remembered, however, that newborn females average approximately 1 cm. less in total body-length than males and that therefore late female fetuses having the same length as males may be somewhat more mature. In Tables VIII, IX and X we have attempted to allow for this difference by making the range of body-length of the females 1 cm. lower in each group than the range of the males of the same group. If these tables are examined it will be noted that even with this correction the percentage frequency of ossification in the females is greater in the majority of instances than in males of the corresponding group. This higher percentage of ossification of the females is particularly noticeable in the shorter and younger groups and in those centers which are not ossified in all cases at birth.

RELATION OF OSSIFICATION TO PARITY

It is well known that both the average weight and the average total length of the newborn of multiparæ is somewhat greater than that of first-born children and this difference has been attributed to a supposed greater length of the prenatal period in the former. *A priori* one might expect to find this greater general development and (supposed) greater maturity accompanied by a more advanced skeletal development. Pryor (1908), however, in his studies on the postnatal ossification of the wrist, found that carpal ossification was more advanced in first-born than in subsequent children. We are certain of the parity of 95 of our cases of which 64 were primiparæ and 31 were multiparæ. The comparative frequency of the ossification centers in these two groups is shown in Table XI below. As will be seen from the examination of this table there are no consistent differences between the two classes with the exception of the os hamatum which was present in 9.4 per cent of the first born and only 3.2 per cent of the later born, and the small number of cases in which the os hamatum occurs makes the significance of this difference quite open to question. In the latter 47.1 per cent of the greatest possible number of centers were present and in the former 47.8 per cent. While the absolute degree of ossification is practically the same in the two classes, it may be suggested that if the supposition is correct that children of multiparae have a longer period of gestation on the average than the children of primiparæ, then ossification is *relatively* more advanced in the latter class. This supposition would be in accord with the observations of Pryor cited above.

VARIATIONS AND IRREGULARITIES IN OSSIFICATION

Taken as a whole, ossification was extremely regular in our material. This falls in line with the experience of Pryor (1908) who has emphasized the regularity of postnatal ossification in the carpus, and with the findings of Pozier (1912) regarding the natal ossification of the knee. The most variable of the bones studied was the cuboid. This bone is generally described as ossifying from 2 to 3 centers. Hasselwander (1909), who has made the most complete study of the ossification of the cuboid, found a single center 24 times in 47 cases, a double center 19 times (in which a possible third was indicated 4 times), and 3 definite centers in 4 cases. In our material the number of centers was much more variable, there being several cases in which 4 or 5 centers were present, and one instance in which 7 ossific granules could be

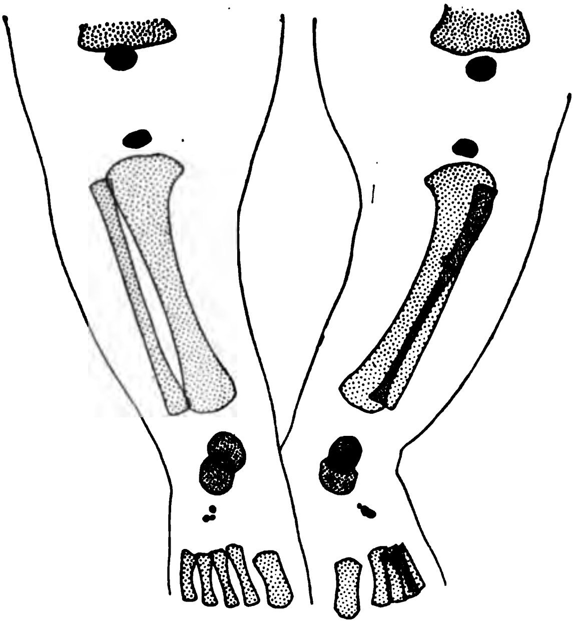

Fig. 6.—Tracing of a radiogram of the lower extremities of a male newborn of 309 days' gestation, having a birth weight of 5060 grams and a total length of 55 cm. Three centers for the cuboid on either side.

recognized. In the young bone the centers appear in the radiograph as a small cluster of minute particles, and the irregular form of this center in older specimens indicates the fusion of these masses which were originally discrete. Quite commonly two or three large centers may be observed for some time after ossification has been in progress, and often the bone has a bifid form in the radiograph. These peculiarities are illustrated in Figs. 6 to 14. We found not only the greatest irregularity in the number and shape of the centers in different specimens but also on the different sides of the same specimen. Examples of this asymmetry are shown in Figs. 7 and 8.

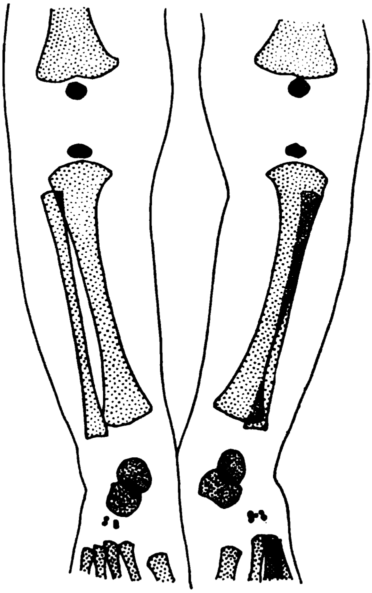

Fig. 7.—Tracing of a radiogram of the lower extremities of a female newborn of 277 days' gestation, having a birth weight of 2710 grams and a total length of 46 cm. Four centers of ossification in the right cuboid, 5 in the left.

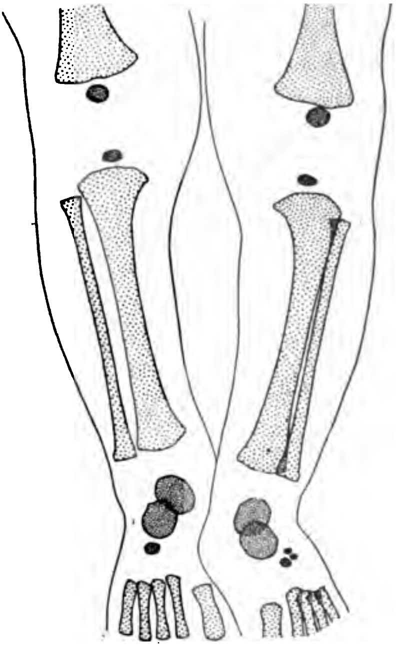

Fig. 8.—Tracing of a radiogram of the lower extremities of a female newborn of 294 days' gestation, having a birth weight of 3525 grams and a total length of 51 cm. One large cuboid center on the right and 3 centers of the cuboid on the left ankle. Knee centers small for a newborn child of this degree of development.

The os capitatum also showed some bilateral irregularity. It was present in three instances on the right side only and in three instances on the left side only. This disagrees with Pryor's finding that the ossification of the wrist is always symmetrical. The os capitatum was double in two cases and in one case it was bifid.

Table XII is arranged to show definitely the percentages of presence and absence of the different ossific centers and to visualize the occurrence and nonoccurrence of each of the centers in relation to the others in the series. This table shows that the inferior femoral center was the one most

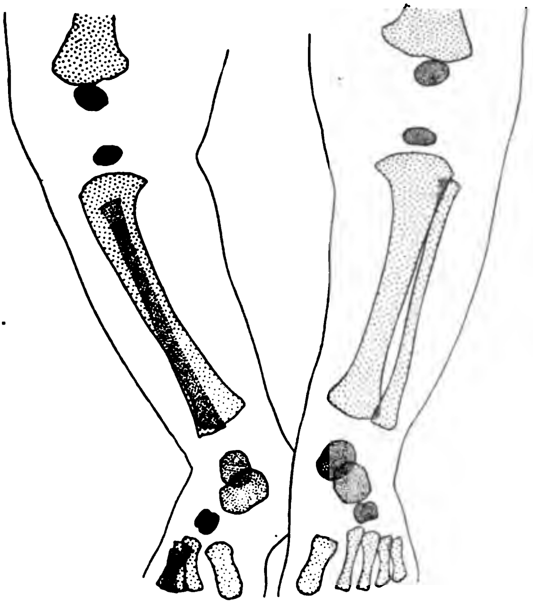

Fig. 9.—Tracing of a radiogram of the lower extremities of a female newborn of 289 days' gestation, having a birth weight of 4155 grams and a total length of 51.5 cm. Large bifed centers of the cuboid on both sides.

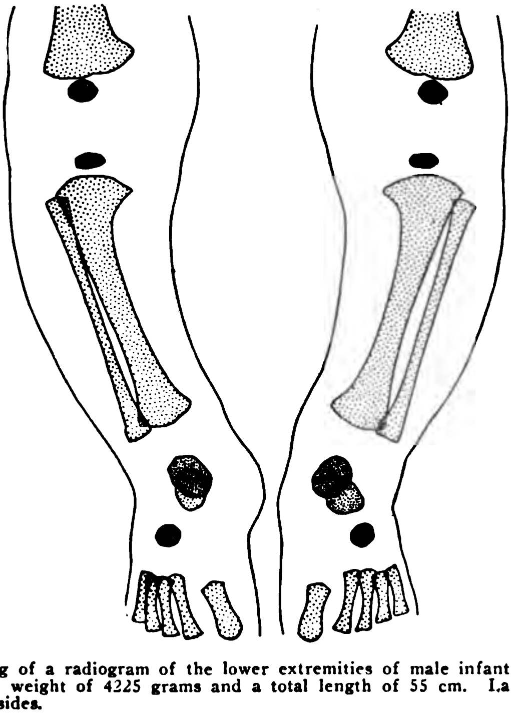

Fig. 10.—Tracing of a radiogram of the lower extremities of male infant of 267 days' gestation, having a birth weight of 4225 grams and a total length of 55 cm. Large single center of the cuboid of both sides.

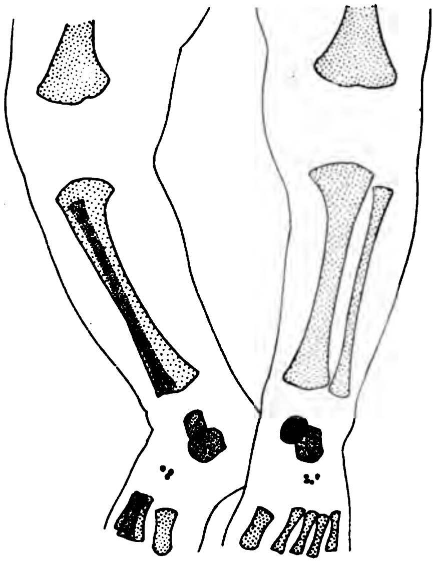

Fig. 11.—Tracing of a radiogram of the lower extremities of a female newborn of 281 days' gestation, having a birth weight of 2185 grams and a total length of 43 cm. No knee centers, but cuboid centers on either side despite a low body weight and body length.

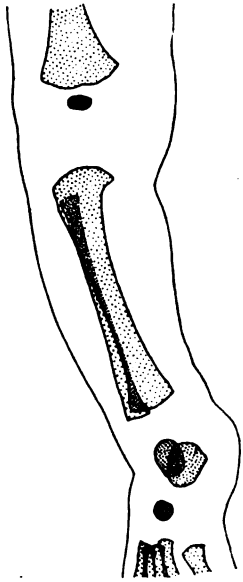

Fig. 12.—Tracing of a radiogram of the right leg of a male newborn of 265 days' gestation, having a birth weight of 3035 grams and a total length of 51 cm. No superior tibial center but a large single cuboid center.

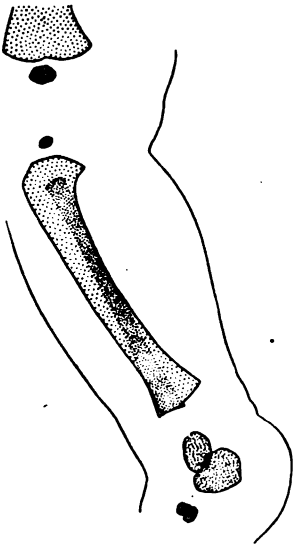

Fig. 13.—Tracing of a radiogram of the right leg of a male newborn of 285 days' gestation, having a birth weight of 4295 grams and a total length of 55 cm. Newborn of unusually large dimensions with relatively small knee centers but highly developed bifid cuboid center.

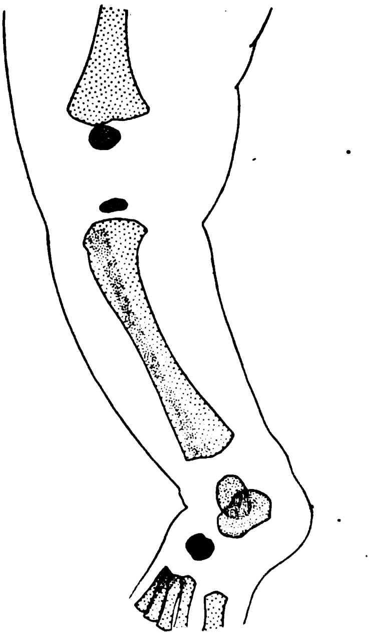

Fig. 14.—Tracing of a radiogram of the right leg of a female newborn of 292 days' gestation, having a birth weight of 4110 grams and a total length of 51.5 cm. Specimen of great weight with advanced development of knee and cuboid centers, the latter being double.

constantly present, being found in 98 of the 100 cases. The other centers were present with varying frequency in association with the inferior femoral, as follows: Superior tibial in 81; cuboid in 37; os capitatum in 15 and os hamatum in 9 of the 98 cases in which the inferior femoral was present. These same centers were absent in a considerable number of those cases in which the inferior femoral was present, as may be seen from the following figures: the superior tibial was absent in 17, the cuboid in 61, the os capitatum in 83, and the os hamatum in 89 of the 98 instances in which the inferior femoral was present. With the exception of the occurrence of the cuboid in one case the other centers were uniformly absent when the inferior femoral epiphysis was not ossified.

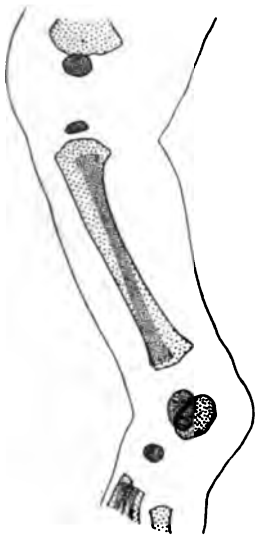

Fig. 15.—Tracing of a radiogram of the right leg of a female newborn of 312 days' gestation, having a birth weight of 3090 grams and a total length of 48 cm.

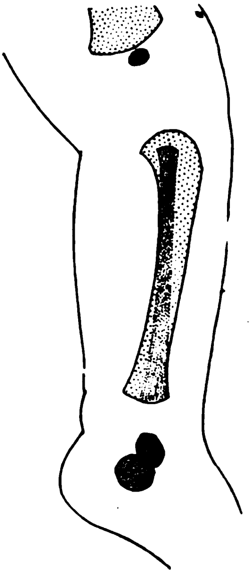

Fig. 16.—Tracing of a radiogram of the left leg of a male newborn of 287 days' gestation, having a birth weight of 3600 grams and a total length of 53.5 cm. A specimen of more than the usual newborn dimensions with no ossification of the cuboid or superior tibial epiphysis.

The superior tibial center was present in 81 cases in which the inferior femoral was constantly present, and the cuboid, capitatum and hamatum occurred 36, 15, and 9 times respectively. This center was absent in 19 cases of the series. In these the inferior femoral occurred in 17 and the cuboid in only 2, and no wrist centers were present. The presence of the cuboid in the absence of the superior tibial epiphysis may be regarded as quite unusual.

The cuboid center appeared 38 times. In these the centers of the inferior femoral, superior tibial, os capitatum and os hamatum were present in the following number of cases: 37, 36, 13, 9. It was never the only center present but was one of only two centers in one instance. The cuboid was absent from 62 cases and in these the inferior femoral was present in 65, the superior tibial in 45, the capitatum in 2 while the hamatum was always absent. The inferior femoral was absent in 1, the superior tibial in 17, the capitatum in 60 and the hamatum in all of the instances (62) where the cuboid was absent.

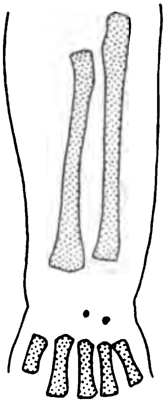

Fig. 17.

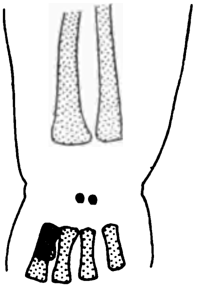

Fig. 18.

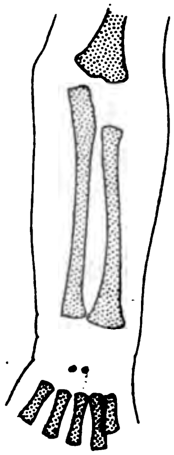

Fig. 19.

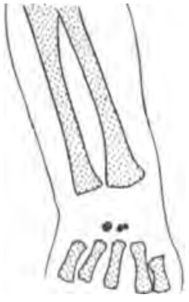

Fig. 20.

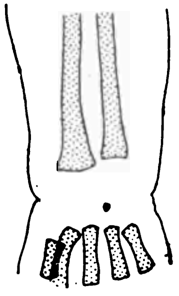

Fig. 21.

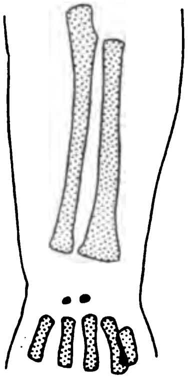

Fig. 22.

Fig. 17.—Tracing of a radiogram of the wrist of a female newborn of 287 days' gestation having a birth weight of 3390 grams and a total length of 53 cm. Os capitatum and os hamatum present.

Fig. 18.—Tracing of a radiogram of the wrist and forearm of a male newborn of 309 days' gestation, having a birth weight of 5060 grams and a total length of 55 cm. An unusually large child with the centers for the os capitatum and os hamatum highly developed.

Fig. 19.—Tracing of a radiogram of the wrist and forearm of a female newborn of 277 days' gestation, having a birth weight of 2710 grams and a total length of 46 cm. Os hamatum and os capitatum.

Fig. 20.—Tracing of a radiogram of the wrist of a female newborn of 312 days' gestation, having a birth weight of 3090 grams and a total length of 48 cm. A small child with large os hamatum and (double) os capitatum.

Fig. 21.—Tracing of a radiogram of the wrist of a female newborn of 289 days' gestation, having a birth weight of 4165 grams and a total length of 51.5 cm. Os capitatum alone present.

Fig. 22.—Tracing of a radiogram of the wrist and forearm of a male newborn of 285 days' gestation, having a birth weight of 4295 grams and a total length of 55 cm. Os hamatum and os capitatum.

The center of the os capitatum was in evidence in 15 cases, in all of which the inferior femoral and the superior tibial centers were present. The cuboid appeared in 12 and the hamatum in 9 of the cases. All of the other centers were present in all of these instances. The os capitatum was seen in no case when the inferior femoral or superior tibial were absent but its presence was noted twice in the absence of the cuboid (which may be considered as somewhat anomalous) and it was present in 6 instances where the hamatum was absent.

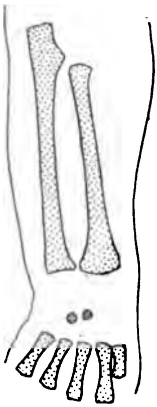

Fig. 23.

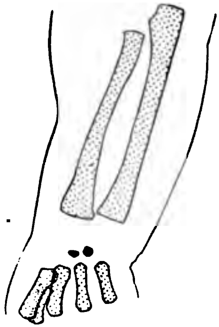

Fig. 24.

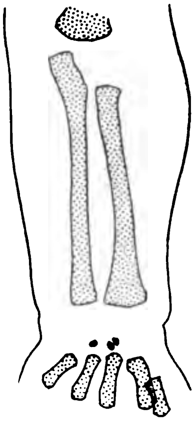

Fig. 25.

Fig. 23.—Tracing of a radiogram of the wrist and forearm of a female newborn of 281 days' gestation, having a birth weight of 3950 grams and a total length of 49 cm. Usually large centers of the os hamatum and os capitatum.

Fig. 24.—Tracing of a radiogram of the wrist and forearm of a female newborn of 292 days' gestation, having a birth weight of 4110 grams and a total length of 51.5 cm. Large os hamatum and os capitatum.

Fig. 25.—Tracing of a radiogram of the wrist and forearm of a male newborn of 267 days' gestation, having a birth weight of 4225 grams and a total length of 55 cm. Os hamatum and (double) os capitatum.

The os hamatum was demonstrable in 9 of our series of cases. All of the other centers were present in every one of these. It was absent in 91 cases, the inferior femoral center was present in all of these, the superior tibial in 81, the cuboid in 38 and the capitatum in 15.

SUMMARY

1. The inferior femoral epiphysis, judging from all available data, is present in about 1 case in 20 in the eighth fetal month, in 1 case in 3 in the ninth month, in 6 cases in 7 in the tenth month, and in about 19 cases in 20 at birth (full-term infants). If not present at birth, the center appears before the close of the first postnatal month. In our own series the center was present in 98 per cent of all newborn children.

2. The superior tibial epiphysis, judging from all available material, is almost never present before the ninth fetal month. It is found in 1 case in 17 in the ninth month, about 2 cases in 5 in the tenth month

and in about seven-eighths of all full-term newborn children. It was present in 81 per cent of the cases in our series.

3. The cuboid, according to all available data, first appears at about the beginning of the ninth fetal month. It is present, on the average,

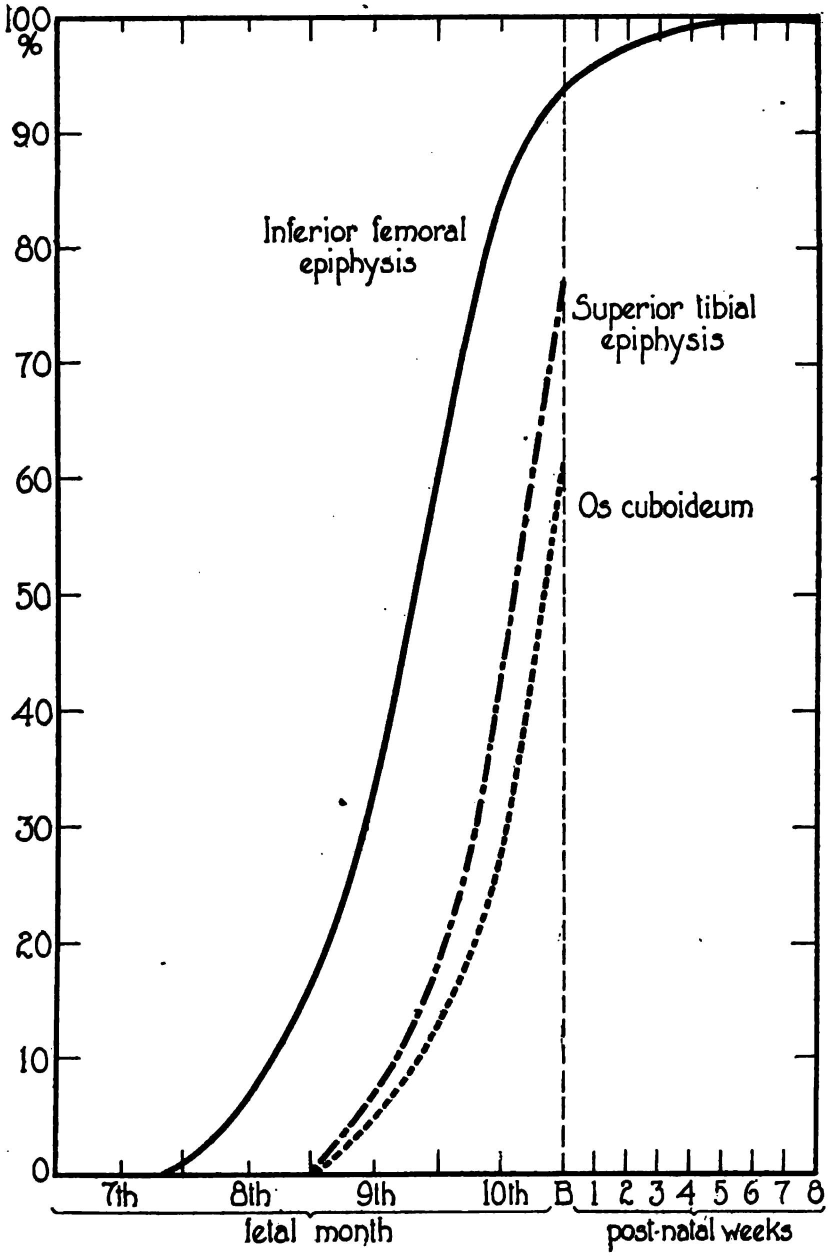

Fig. 26.—Graphs illustrating the frequency of ossification of the inferior femoral epiphysis, the superior tibial epiphysis and the os cuboideum in later fetal life. Abscissae, age. Ordinates, frequency of ossification in per cent. (Based on the material presented in Tables I, II, and III.)

in about 1 case in 25 in the ninth month, in about 1 case in 4 in the tenth month, and in about 3 cases in 5 in full-term newborn children. In our own series the center was present in a much smaller per cent of all cases than is reported by other investigators (38 per cent).

4. Two carpal ossification centers, those of the os capitatum (os magnum) and of the os hamatum (unciform), may be present in the newborn. In our series the os capitatum was present in 15 per cent and the os hamatum in 9 per cent of all cases.

5. There is a close relation between total body-length and frequency of ossification of the several centers discussed in this paper. A similar, but less close, correlation exists between frequency of ossification and the body-weight.

6. In our material the correlation of body-weight, total body-length and frequency of ossification with menstrual age was quite close for the middle members of the series ranging in menstrual age from 270 to 300 days. But the outlying cases (having a menstrual age of less than 270 or more than 300 days) show little relation between these measures of bodily development and age as determined from the menstrual history.

7. Our evidence points to the conclusion that ossification proceeds slightly more rapidly in females than in males during intrauterine life even though the weight and dimensions of the females are less than those of the males.

8. Our observations show no direct evidence of any relation between parity and the rate of ossification in intrauterine life.

9. Variations in the *number* of ossification centers present for individual bones were limited to the os capitatum and os cuboideum. The latter is formed from an extremely variable number of centers. When anomalies in the number of centers are present they are often asymmetrical.

10. Variations in the order of appearance of centers were decidedly unusual in our material, being confined to premature ossification of the os cuboideum (2 cases) and of the premature ossification os capitatum (2 cases).

11. The usual order of appearance of the centers under consideration is as follows: (a) Inferior femoral epiphysis; (b) Superior tibial epiphysis; (c) Cuboid; (d) Os capitatum; (e) Os hamatum.

LITERATURE

Barkow, H. C. L.: Über das Vorkommen von Knochenkernen in den knorpligen Epiphyse der langen Knochen mit Beziehung auf Würdigung der Lebensfähigkeit derselben in forensischen Verhandlungen. Vierteljahrsschr. f. gerichtl. Med., 1872, xvi. **Béclard, P.:** Nouveau Jour. de Méd., Chir. et Pharm., 1819, iv, p. 107 et seq. **Böhm:** Ueber die forensische Bedeutung des Knochenkerns in der unteren Epiphyse des Oberschenkels der Neugeborenen. Vierteljahrsschr. f. gerichtl. Med., 1858, xiv. **Brice, T. H.:** Quain's Elements of Anatomy, 1915, vol. iv, Pt. I (Eleventh Ed.), London. **Casper, J. L.:** Praktisches Handbuch der gerichtlichen Medicin, 1856. (New Sydenham Society's Translation of 1869 consulted.) **Corrado, G.:** De' principali nuclei di ossificazione che possono rinvenirsi all' epoca della nascita. L'Anomalo, 1891, iii, 231 to 244. Cory, R.: Notes on the Examination of the Bodies of Fifty Children Born Dead or Shortly Dying. St. Thomas's Hosp. Rep. (1877), N. S., 1878, viii, 61 to 74. Notes on the Examination of the Bodies of Fifty Children Born Dead or Shortly Dying. (Second series.) St. Thomas's Hosp. Rep. (1879), N. S., 1880, x, 263 to 276. Notes on the Examination of the Bodies of Fifty-eight Children Born Dead or Shortly Dying. (Third series.) St. Thomas's Hosp. Rep., N. S., 1897, xxiv, 131 to 150. Debierre, C.: Contribution à l'étude de l'ossification et de l'homotypie des pièces du carpe et du tarse chez l'homme. Journ. de l'Anat. et de la Physiol., 1886, xxii. Freymond, P. L. A.: Etude sur l'ossification des os du pied, faite d'après la radiographie. Thèse, Bordeaux, 1910. Filomusi-Gullfi, G.: Sul nucleo epifisario femorale. Boll. Soc. med. chir. Pavia, 1889, No. 2, 25 to 27. Fujinami, K.: Ueber die Ossifikation der Handwurzelknochen. Fortschr. a. d. Geb. Röntgenstr., 1911, xvii, 311 to 318. Graham: The Center of Ossification in the Lower Femoral Epiphysis in Relation to Forensic Medicine. Diss. Berlin, 1886. Guichard, A.: De la valeur medico-legale du point de Béclard, point d'ossification de l'extrémité inferieur du femur. Thèse, Lyon, 1905, 83 pp. Hahn, H.: Röntgenographische Untersuchungen über das Verhalten der Epiphysen der Unterschenkelknochen wahrend des Wachstums. Festschr. 70. Geburtsh. C. v. Kuppfer, 1899, iii, 731. Hartmann, G.: Beiträge zur Osteologie der Neugeborenen. Diss. Tubingen, 37 pp. 1869. Hasselwander, A.: Untersuchungen über die Ossification des menschlichen Fussskelets. Zeitschr. f. Morphol. u. Anthropol., 1909, xii, 1 to 140. Hassenstein, W.: Zur Reifebestimmung des Foetus aus dem Knochenkern der Oberschenkelepiphyses. Zeitschr. f. Medizinalbeamte, 1892, v, 129 to 132. Heimann, A. und Potpeschnigg, K.: Über die Ossification der kindlichen Hand. Jahrb. f. Kinderheilk., 1907, lxv, 437 to 456. Hess, J. H.: The diagnosis of the age of the fetus by the use of roentgenograms. Am. Jour. Dis. Child., 1917, xiv, 397 to 423. Kjölseth, M.: Untersuchungen über die Reifezeichen des neugeborenen Kindes. Monatschr. f. Geburtsh. u. Gynäk., 1913, xxxviii, (Ergänzungsh.), 216 to 298. Leopold, G. and Leisewitz, T.: Geburtshilflicher Röntgen-Atlas. Dresden, 1909. Long, E. and Caldwell, E. W.: Some Investigations Concerning the Relation Between Carpal Ossification and Physical and Mental Development. Am. Jour. Dis. Child., 1911, i, 111 to 138. Mildner, E.: Ueber die Benützung des Knochenkernes in der unteren Epiphyse des Schenkelbeins zu gerichtsärztlichen Zwecken. Vierteljahrsschr. f. prakt. Heilk., 1850, vii, 39 to 44. Nicolai, J. A. H.: Beschreibung der Knochen des menschlichen Foetus. Regensberg, 70 pp. 1829. Nomballais, J. M. E.: Contribution à l'étude de l'ossification des os du carpe d'apres la radiographie. Thèse, Bordeaux, 36 pp. 1909. Olivier, C. P.: Annales d'Hygiéne publique, xxviii, 342. Pleissner, H.: Nonnulla de ossificatione in femoris inferiore epiphyse. Diss. Lipsiae, 22 pp. 1861. Pozier, J.: Etude radiographique de l'ossification du genou chez le nouveau-né. Thèse, Paris. 1912. Pryor, J. W.: The chronology and order of ossification of the bones of the human carpus. Bull. of the State Univ., Lexington, Ky., 1908. Puyhaubert, A.: Recherches sur l'ossification des os des membres chez l'homme. Journ. de l'Anat. et Physiol., 1913, xlix, 224 to 268. Rambaud et Renault: Origine et développement des os. Paris, 1864. Rotch, T. M.: A Study of the Development of the Bones in Childhood by the Roentgen Method, with the View of Establishing a Development Index for the Grading of and the Protection of Early Life. Trans. Am. Physicians, 1909. Rotch, T. M.: A Comparison in Boys and Girls of the Same Height, Weight and Epiphyseal Development. Arch. Pediat., 1910, xxvi, 567 to 569. Sappey, M. P. C.: Traité d'anatomie descriptive. (Ed. 2), T. I. 1867. Tamassia, A.: Sul centro d'ossificazione dell'epifisi inferiore del femore, dell' astragalo e del calcagno. Atti R. Inst. Veneto di Sci. Lett. ed Arti, 1893, 7 ser., iv, 815 to 828. Toldt, C.: Die Knochen in gerichtsärztlicher Beziehung. In: Maschka: Handb. d. gerichtl. Med., Bd. iii, 483 to 585, 1882.

THE EFFECTS OF INANITION IN THE PREGNANT ALBINO RAT, WITH SPECIAL REFERENCE TO THE CHANGES IN THE RELATIVE WEIGHTS OF THE VARIOUS PARTS, SYSTEMS, AND ORGANS OF THE OFFSPRING*

LEE W. BARRY

That a restriction of the diet of the mother during pregnancy usually results in a decrease in the weight of the offspring has long been known. Prochownick (1899, 1901) obtained a marked reduction in the weight of the human newborn by a restriction of the mother's diet during the last weeks of pregnancy. Rudolski (1893) starved rabbits and a dog during pregnancy and noted a reduction in the size of the offspring. Paton (1903) underfed pregnant guinea-pigs and obtained a marked reduction in the weight of the young. Reeb (1905) underfed rabbits and dogs during pregnancy and obtained young greatly reduced in weight. However, none made observations on the changes in the relative weights of the various organs, systems, and parts of the newborn which might occur during inanition of the pregnant mother. The main object of this investigation, therefore, is to show the effect of inanition in the pregnant albino rat on the changes in the relative weights of the various systems, organs, and parts of her newborn. Observations were made also on the possibility of blighting of the ovum, death of the fetus *in utero*, prolongation of gestation, abortions, and premature deliveries during inanition of the mother.

MATERIALS AND METHODS

For the present investigations, two series of adult female rats (*Mus norvegicus albinus*) were used for inanition during pregnancy. Those in series A are adult females from the colony at the Institute of

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Anatomy, which were kindly given over to my use by Dr. C. M. Jackson; Series B consists of adult females from several sources. A few were reared from normal litters in Series A; some were purchased from a local animal dealer, and others were obtained from the departments of physiology and psychology of the University. Unfortunately, however, the exact age of very few of the females was known.

Breeding.—Since the influence of inanition on the length of gestation was to be noted, and in order to exclude the possibility of some of the small rats being the result of premature birth, it was very important to know the approximate date of copulation.

Three methods were used:

1. Kirkham and Burr (1913) have shown that the female albino rat usually ovulates within twenty to forty-eight hours after the birth of a litter, and impregnation occurs one to four days after the casting of a litter. A few of my females became pregnant by this method, the males being left with the mother during the second night following delivery. This method was abandoned, however, since out of a very large number of females delivering only a few became pregnant.

2. The second method was to place several males alone in small wire cages and once each day the different females were placed with the males. If the female was in heat, copulation usually took place at once. The female was not removed at once, but was left with the male for a period varying from fifteen minutes to one hour. If not in heat, the female usually resented the advances of the male, in which case she was removed and replaced by another female. After successful pairing with the male, the female was weighed. Her weight, together with her number, was recorded, and she was placed in a cage with other females that had paired. It was found better to place the female in with the male, because when the process was reversed the male, suddenly finding himself thrust into a strange cage, paid very scant attention to the female, but would spend all his time attempting to escape from the cage. The majority of the females were paired by this method.

3. The third method employed consisted in placing several males in a cage with a number of females. They were left together constantly and inspected at intervals of six hours during the day and once, in the evening. When a female in the cage became in heat, the males would copulate with her with such frequency that in a short time the vagina became distended, reddened, and at times bled slightly. After a

little experience, the females that have copulated may be distinguished by the distended, reddened, and at times slightly bloody vaginal orifice.

Period and severity of starvation.—In the beginning of the investigations it was decided to starve one group of females throughout pregnancy and another group during the last half only. The results from starvation were so disappointing that this was abandoned. Of seventeen females that had been observed to copulate and were starved from this time for periods varying from sixteen to twenty-six days, only one gave birth to a litter, four died, and the others were so weakened that they were saved only with difficulty. In the second group fifty-nine females were starved severely during the last half of pregnancy (or suspected pregnancy), beginning on the eleventh day after copulation. The animals were weighed daily and their weights recorded. The amount of food (usually not more than 1 gm.) which they received daily varied with their loss in weight and general condition. The food consisted of whole-wheat bread (graham) soaked in whole milk (Table 1). Water from the city supply was allowed in the cages at all times.

Prevention of mother's eating young.—A difficulty soon experienced was the eating of the young by the starving mothers. Early in the investigation several of the mothers ate and mutilated their newborn young, rendering them worthless for dissection purposes. Various muzzles were devised but without success. The method finally adopted was to place the pregnant female in a cage with a wire bottom, the meshes of which were 1 cm. square, thus allowing the newborn rats to drop through onto a clean piece of paper beneath. Thus, not only were the newborns saved for dissection, but any abortions or premature deliveries might be noted.

Throughout the period of inanition the pregnant females were kept in a specially warmed room in order to prevent death from chilling or pneumonia.

Necropsies.—In this investigation ninety-nine rats were necropsied, sixty of which were from mothers underfed during the last half of pregnancy, twenty-nine were normal fetuses removed from the recently killed mother, and ten were normal newborns. In order to compare the effect of prenatal inanition in the newborn rat (test), it was necessary to compare this test rat with a normal (control) fetus of the same body-weight from an unstarved mother.

The mothers from which the control fetuses were obtained were chloroformed. After death the abdomen was slit open and the fetuses and placentas removed from the uterine horns. The fetus was removed from the amniotic sac and the umbilical cord severed by crushing in order to prevent bleeding, close to the belly wall. The fetus was quickly wiped dry of excess fluid, killed by chloroform, measured, weighed, and dissected. These are designated the "prenatal controls." The "test rats" are newborn rats from the underfed mothers. The "normal newborns" are newborn rats from normal litters.

The series and number of the mother, the number of the litter, and the order in the litter for each individual dissected is shown in Table 4. A or B with the number following denote the series and number of the mother in the series; the number following this denotes the number of litters the mother has borne during the experiment, while the number following the decimal point denotes the number of the individual rat in the litter. For example, B2–2.1 shows that the rat was number 1 in the second litter from the mother number 2, Series B.

It will be noted that these rats (Table 4) are arranged in five groups in accordance with their net body-weights. Group 1 contains the test rats and prenatal controls whose net body-weights range from approximately 2 gm. to 2.5 gm.; Group 2, those ranging from 2.5 gm. to 3 gm.; Group 3, those ranging from 3 gm. to 3.5 gm.; Group 4, those ranging from 3.5 gm. to 4 gm., and Group 5, those ranging from 4 gm. to 4.5 gm. This grouping was done in order to facilitate computations and to render apparent any variations according to the size of the rats. Since no sexual differences were found in the organs and parts, the sexes are combined in the groups and computations. All computations were made on the average weights of the organs and parts.[1]

All the test rats necropsied were born by the natural method, although the length of gestation was occasionally prolonged.

The necropsy technic was the same as that described by Jackson and Lowrey (1912) and Jackson (1913), with a few modifications. Their technic was as follows:

After killing with chloroform, the gross body-weight and lengths of body (nose-anus) and tail were recorded. The head was removed on a plane just anterior to the larnyx and posterior to the cranium, and weighed. The trunk was suspended, thus allowing the blood (unmeasured) to escape. The eyeballs and brain were then removed and placed in a moist chamber. The trunk was next dissected and the viscera removed and weighed individually in the following sequence: thyroid gland, thymus, heart (opened and blood clots removed), lungs, liver, spleen, stomach and intestines (including contents, mesentery and pancreas, also weighed without contents), suprarenals, kidneys, gonads, and spinal cord. The extremities were removed at the shoulder and hip joints and weighed. The skin was next removed from the trunk and extremities and weighed; the skeleton and musculature were weighed together; then the musculature was dissected off and its weight determined by subtracting the weight of the skeleton from the combined weight. As soon as possible after the birth of the inanition test-rats, and immediately after the removal of the prenatal controls from the mother, they were killed by chloroform, if not already dead. Each was then placed on its back and extended by allowing one end of a steel ruler (300 mm. by 35 mm. by 2 mm., weight 263.5 gm.) to rest on the abdomen and neck. In this way the amount of extension was found to be much more constant than by trying to hold the body extended by means of the hand. The distance from the tip of the nose to the anus (nose-anus length) and from the tip of the tail to the anus (tail-length) was carefully measured by calipers and the distance read off on a millimeter scale.

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[1] The original individual data are filed and available for reference at the Wistar Institute of Anatomy, Philadelphia.

Jackson and Lowrey weighed the stomach, intestines, and pancreas together with the mesentery. In my investigation, however, the stomach, intestines, and pancreas were weighed separately. The technic was as follows:

The rat was placed belly down and the skin, muscles, and other tissues dissected from the left lumbar region and an incision made through the peritoneum just below the costal margin. By gentle pressure on the abdomen, the stomach, spleen, and part of the pancreas were forced through the opening. The spleen was now easily separated from the stomach and pancreas and placed in a moist chamber. The stomach was freed from its attachments to the liver and pancreas, seized at its juncture with the esophagus with a small pair of forceps, firmly compressed to prevent the escape of any of the gastric contents, and severed at that point and also at the pylorus. The stomach was then weighed in a closed container, opened, its contents allowed to escape, and the interior cleaned with moist filter paper, after which it was reweighed. The intestines were removed as described by Jackson and Lowrey (1912) and weighed with and without their contents, after the pancreas had been removed. By subtracting the weight of the contents from the body-weight, the net body-weight was obtained, and this was used as a basis for computations.

It was found that the "gold dust" preparation, used by Jackson (1915) to free the skeleton of its periosteum and ligaments, acted too strongly on the delicate skeletons in my series, resulting in a loss of the cartilages. Consequently, the skeletons were cleaned as thoroughly as possible of muscles and ligaments merely by dissection. These are designated as "moist" skeletons. The moist skeletons were dried for one month (to a constant weight) in an oven at a temperature of 85°C. to 95°C. to obtain their dry weight.

GENERAL EFFECTS OF UNDERFEEDING

Blighting of ovum.—In one experiment seventeen female albino rats were underfed for varying periods of from sixteen to twenty-six days from the time of observed copulation. Only one (A 6) gave birth to a litter after twenty-four days. This mother received daily 10 gm. of food until the eleventh day after copulation, and thereafter 1 gm. daily until delivery, starvation being severe only in the last half of pregnancy. Her fetuses were necropsied and included with the data. Of the seventeen rats, four died of starvation. Necropsy revealed no pneumonia or other disease.

In another series fifty-nine females were underfed from the eleventh day after copulation to delivery, death, or the discovery of no existing pregnancy. Of this number, nineteen (32 per cent), (Table 1), gave birth to litters; twelve (20 per cent) died during pregnancy (Table 2); and twenty-seven (46 per cent) did not give birth to litters (Table 3).

Huber (1915) found in the rat on the sixth day after copulation, localized thickenings of the uterine mucosa, sufficient to cause localized swellings of the uterine tube. Stotsenburg[42] (1915) has shown that on the thirteenth day of pregnancy the average weight of the rat fetus is 0.040 gm. It is interesting to note that in my pregnant rats it was found that the swellings in the uterine horns could be palpated through the abdominal wall of the living animal between the tenth and eleventh days after copulation. None of the females (sixteen) underfed from the time of copulation, and not having litters, showed swellings in the uterine horns at any time palpable through the abdominal wall. In the twenty-seven females (Table 3) observed to copulate and underfed from the eleventh day thereafter (no litters resulting), swellings in the uterine horns were palpated in fifteen, doubtful swellings in three, and no swelling in nine. Of the twenty-seven animals, five died during the starvation period; four of these were necropsied, one (A 63) showed definite swellings in the uterine horns (two in the right, and three in the left, about 8 mm. in diameter), the other three showed no macroscopic evidence of pregnancy.

Microscopic examination of sections of the uterine swellings in A 63 revealed a mass of degenerating tissue with no evidence of a fetus. One female, B 64, was refed ten days after being underfed twelve days and was killed. At necropsy four swellings in the left and five in the right uterine horn were found, averaging about 1 cm. in diameter. Microscopic examination of these showed a mass of degenerating tissue with no evidences of fetal tissue. Apparently these were cases of blighted ova or early embryos. What was the fate of the swelling palpated in the other rats starved? Were they absorbed? This question needs further investigation.

It is significant to note that of the seventeen females starved from the time of copulation, only one became visibly pregnant and no swellings were ever palpated in the remaining sixteen. Does starvation early in pregnancy inhibit implantation by lessening the amount of pabulum or embryotroph necessary to the nourishment of the ovum, or by uterine circulatory changes or a condition of acidosis? Or does it cause a blighting of the ovum after implantation? This also needs further investigation.

Length of gestation.—According to Stotsenburg[41] (1914), the length of gestation in the non-lactating albino rat varies from twenty-one days and fifteen hours to twenty-two days and sixteen hours. The length of gestation in my starved rats varied from twenty-one days to twenty-six days; eight of the total of twenty-two were above the twenty-three-day limit, six with a gestation-period of twenty-four days, one of twenty-nine days, one of twenty-six days. Thus, severe inanition during the last half of pregnancy usually lengthens the duration of gestation comparatively little. This is rather surprising, in view of the fact that King (1913) found the gestation period markedly lengthened in pregnant nursing rats. King says:

> "The period of gestation is always prolonged when a female is suckling six or more young. In these cases the number of young in the second litter seems to have less influence on the length of the gestation period than has the number of young suckled, but if both litters are very large, the gestation period may be extended to thirty-four days."

Daniel (1910) in investigations on the mouse, formulated the following law (quoted by King, 1913, as "Daniel's law"): "The period of gestation, in lactating mothers, varies directly with the number of young suckled."

Both Daniel and King seem to have overlooked the work on the prolongation of gestation in different species of rats by Lataste (1891), in which he states:

> "On voit que, d'une facon générale et sauf perturbations accidentelles, le retard de la gestation, dans une même espèce, est proportionnel au nombre des petits allaités, un nouveau jour de retard correspondant à un nourisson de plus."

He proved that the retardation of gestation was due to a delay of the implantation of the ovum during the first six to ten days of pregnancy, due probably to a lack of proper nourishment for the ovum as it enters the uterine cavity. He found that traumatizing the mother early in pregnancy markedly prolonged gestation, while at later periods there was no effect. This is in harmony with my observation that there is very little prolongation of gestation in starvation during the latter half of pregnancy.

Abortion and premature delivery.—Although my females were kept in cages with meshed-wire bottoms, so that the products of conception might fall through, no abortions or premature deliveries were observed. Rudolski (1893), in inanition experiments on rabbits and a dog, stated that premature deliveries seldom occurred, and that abortions were never observed. Prochownick (1901) cites forty-eight cases in which women were placed on a restricted diet during the last half of pregnancy, with no abortions or premature deliveries resulting. He also reviewed the earlier literature on the subject. Paton (1903) observed no abortions or premature deliveries in guinea-pigs starved during pregnancy. Reeb (1905) observed premature deliveries in two rabbits starved from the beginning of pregnancy, but none in rabbits or dogs starved during the last half of pregnancy.

Although no abortions or premature deliveries were observed, it is interesting to note that five of the twelve females that died during pregnancy (Table 2) began to bleed from the vagina from one to three days before the end of the normal gestation period. In one of these, B 64, the fetuses had evidently been dead for some time, since on section and microscopic examination of the swellings in the uterine horns, a degenerating mass of material was found, in which no fetal structures were distinguishable. Rat B 58 (Table 2), killed after refeeding ten days, showed a similar condition in the uterine horns; but the death of the fetuses evidently occurred earlier, as the swellings of the uterine horns were smaller (5 mm. to 8 mm. in diameter, compared to 9 mm. to 15 mm. in diameter in B 64).

Macroscopic examination of the placentæ of the rats dying after hemorrhage revealed no separation of the placentæ and no evidence of beginning labor. Are these cases to be regarded as beginning abortions in which the fetuses have died *in utero* and therefore analogous to missed abortions occurring in the human being? This subject requires further investigation, checked by careful microscopic examination to determine whether this bleeding is due to beginning abortion or is the result of degenerative changes in the placenta itself, or perhaps to changes in the maternal blood.

Sterility.—From the total number of seventy-six female rats starved during pregnancy (or suspected pregnancy), only four became pregnant a second time (B 2, B 29, B 43, and B 44, Tables 1, 2, and 3). Of the seventy-six starved, twenty-one died, a mortality of 27 per cent. Although the remaining fifty-five were placed with the males frequently, only four (7 per cent), became pregnant after starvation. Thus it appears that inanition during pregnancy produces a condition of sterility in the majority of the females. Whether this sterility is absolute or only temporary can not be stated, because a sufficient period has not elapsed since the starvation of many of the females.

Jackson and Stewart (1919) likewise found that starvation in young female rats produced sterility in a large number.

Stillbirths and viability of the newborn.—From the data in Table 1, it is seen that from a total of 129 newborn young rats from mothers starved during pregnancy, forty-one were found dead after delivery. Whether these were dead *in utero*, died during delivery, or afterwards, it is impossible to state. At birth, the newborn dropped through the wire bottom of the cage, and as many were born inclosed within the amniotic sac, death may have resulted from suffocation. The living seemed to be quite vigorous. As they were necropsied as soon as possible after birth, no statements can be made concerning their viability and after-life. King (1916), however, has made a study of the growth of albino rats undersized at birth (one a female weighing but 2.6 gm.). She states:

> "A very small weight at birth indicates that a rat has a handicap in its organization, that environment, however favorable, can not overcome. Such animals, although they appear vigorous and healthy during their growth period and after reaching the adult state, are unquestionably subnormal in regard to the size of the body and the central nervous system."

Size of litters.—The average number of young per litter observed in the rats starved during pregnancy was 5.9. King (1915) found an average of 7.0 per litter in 1,089 litters. Apparently starvation during the last half of pregnancy has at least no marked effect on the number of young per litter.

Weight of fetus.—Rudolski (1893) starved rabbits and a dog during pregnancy and found that on one-half to one-third of their normal diet the mothers gave birth to healthy, normal offspring and that at times these litters even exceeded in weight the litters from mothers on a normal diet. However, on greater reduction (one-fifth to one-thirtieth) of their normal diet, the mothers gave birth to young many of which were born dead or died soon after birth. The body dimensions were reduced in size. The offspring were toothless and gelatinous in structure, showing a poor development of the subcutaneous tissues and a marked reduction in the amount of fat.

Prochownick (1901), in a report of forty-eight cases in which women with contracted pelves were placed on a restricted diet during the last months of pregnancy, found the weight of the newborn to be markedly reduced. The average birth-weight was 2,960 gm. and 2,735 gm., respectively, in twenty-four males and twenty-four females. Thus, the males were 11 per cent to 14 per cent and the females 14 per cent to 15 per cent below the average weight for that part of Europe (Hamburg). The length, head circumference, and ossification of the cranial bones were not affected. There was, however, a reduction in the amount of subcutaneous fat.

Paton (1903), in a series of female guinea-pigs kept on a low diet during pregnancy, found the average weight of the litters to be 28 per cent below that in mothers kept on a normal diet.

Reeb (1905) obtained a marked reduction in the size of the young in rabbits and a dog placed on a reduced diet during the last half of pregnancy. Although the pregnant rabbits suffered an average loss of but 7.1 per cent in body-weight during inanition, the individual newborn showed a reduction of 20 per cent to 60 per cent in weight as compared with young from the same mothers on a full diet. The dog lost 8.1 per cent during starvation in pregnancy and the individual young showed a loss of 29 per cent as compared with controls from the same dog on a normal diet.

All the experiments were carried out by a quantitative reduction in diet. Evvard (1912), however, has shown that undersized young with lessened vigor and vitality result when young pregnant sows (gilts) are fed on corn alone, in large quantities, but unsupplemented by a diet rich in ash and protein. He attributes this reduction in size and vigor of the offspring chiefly to a lack of calcium salts in a diet of corn alone. Later, Evvard, Dox, and Guernsey (1914) found that normal litters resulted if the corn diet was supplemented by calcium chloride (or calcium carbonate) and blood protein.

Hart, McCollum, Steenbock, and Humphrey (1919) fed a diet of corn, grain, and wheat straw to pregnant heifers. The resulting offspring were weak and often dead-born. However, when a suitable salt mixture was added to the diet, normal calves resulted. Osborne and Mendel (1914) have shown that the corn kernel is deficient in certain salts and amino acids which are necessary to normal growth in the rat.

From my data on the weights of individual rats from mothers starved during the last half of pregnancy, the average gross weight of the newborn is approximately 3 gm. The average gross weight of the normal newborn rat in the same dolony has beed found to be approximately 5 gm. (Stewart, 1919), the average in my ten normal newborn being 4.92 gm. Consequently, underfeeding during the last half of pregnancy apparently causes a reduction of about 40 per cent in the average birth-weight of the newborn albino rat. The gross body-weight of the individual test rats ranged from 2.1 gm. to 4.4. gm. The average percentage loss of weight of the mother during starvation (Table 1) was 28 per cent, the loss ranging from 11 per cent to 39 per cent. There is no constant relation between the loss in body-weight of the mother and the size of the newborn or the number in the litter. However, it should be noted that in general the percentage loss of weight was greatest in the heaviest rats which requently bore the heaviest fetuses. Also, as might be expected, the weight of the newborn tends to be inversely proportional to the loss in the weight of the mother. Thus, the heaviest newborns (4.3 gm.) were from a mother losing only 11 per cent in weight.

Just what effect this loss or retardation in birth-weight has on the relative weights of the various parts, systems, and organs of the newborn rat, or other animals, has not hitherto been ascertained, so far as appears from the available literature. These effects of prenatal starvation, and a comparison of the results obtained in postnatal starvation, will now be considered for the various organs and parts. In each case the data for the normal newborn will be given first; then the prenatal norm, and finally the condition in the corresponding groups of test rats will be compared. This will enable us to see whether, in these stunted test rats with retarded body-weight, the various parts retain their normal proportions, as found in the normal, younger, fetuses of the same body-weight; or, if not, the character and extent of the disproportions which have arisen. Finally, a comparison will be made with the known effects of postnatal inanition.

RELATIVE WEIGHTS AND LENGTHS OF BODY PARTS

Ratio of body-weight to body-length.—In the ten normal newborn rats dissected, the average body-length was 51 mm., net body-weight 4.92 gm.; Stewart (1919), using litters from the same colony, found the average body-length to be 50.3 mm., net body-weight 5.03 gm.

The ratio of the body-weight in grams to the body-length in millimeters in my newborns was 0.096. In Stewart's series (1919) the ratio is 0.099. The Wistar norm ratio (Donaldson, 1915) is 0.10 for a 51 mm. rat. In my prenatal fetal controls (Table 5), the ratio of the body-weight to the body-length is 0.061 in Group 1, and increases through all the groups until in Group 5 it is 0.092. The ratio for the test rats in Group 1 is 0.061 and increases through all the groups at nearly the same rate as the prenatal controls to 0.089 in Group 5.

By comparing the prenatal and newborn norms, it is found that the smaller the fetus *in utero*, the smaller is the figure representing the body-weight to body-length ratio; in other words, the younger the fetus (from 2 gm. to 4.1 gm.), the less the weight per millimeter of body-length. The test rats follow this same law, the ratio being very similar to that in the corresponding normal controls of the same weight or length. Therefore, it may be stated that the growth ratio, or the relation between fetal body-weight and body-length, is not disturbed by starving the mother during pregnancy.

Ratio of tail-length to body-length.—The ratio $\frac{\text{tail-length}}{\text{nose anus length}}$ is called the "tail ratio." In my normal newborns the tail ratio $\frac{\text{tail-length, 16.4 mm.}}{\text{body-length, 51 mm.}}$ is 0.311 (sexes combined). Stewart (1918*a*), in litters from the same colony, found a tail ratio of 0.318 (sexes combined). Jackson (1915*a*), using litters from both Minnesota and Missouri, found a tail ratio of 0.36 in the newborn (sexes combined). The tail ratio for the prenatal controls in Group 1 is 0.339 (all females); for the test rats, 0.324; for the controls in Group 2, 0.288, for the test rats, 0.310; for the controls in Group 3, 0.313, for the test rats 0.327; for the controls in Group 4, 0.300, for the test rats, 0.326; for the controls in Group 5, 0.296, and for the test rats, 0.323. The tail ratio for the prenatal norm averaged for all five groups is 0.307; for the test rats, 0.322. From these data it is apparent that the ratio of the tail-length to the body-length during the later prenatal growth of the rat (from 2 gm. to '.1 gm.) is about the same as that found at birth; also that inanition in the mother during pregnancy has very slight influence on the tail ratio of the offspring.

If the absolute data are directly compared, the tail-length in the test rats in all the groups (Table 5) is slightly above that of the prenatal norms of the same average body-weight, being 2.8 per cent above in Group 1 and 13.1 per cent on Group 5, showing an average gain of 6 per cent above the norm in all the groups combined. This gain in tail-length, therefore, appears to be less marked in the smaller rats, becoming greater as the size of the body approaches that normal at birth. It agrees with the observations of Jackson[19] (1915) and Stewart (1918), that postnatal starvation in growing rats tends to produce relatively long-tailed individuals.

Head.—Jackson and Lowrey (1912) give the weight of the head in the newborn albino rat as 1.147 gm., or 21.65 per cent of the body-weight, 5.3 gm. (sexes combined). In my normal newborn series the weight of the head is 1.041 gm., or 21.2 per cent of the body-weight, 4.92 gm.

In my prenatal controls, the average weight of the head forms 24.2 per cent, 23.0 per cent, 22.7 per cent, 21.0 per cent, and 20.5 per cent of the body-weight in Groups 1, 2, 3, 4, and 5, respectively (computed from Table 5). Thus, in the prenatal controls the head has a higher relative weight in the smaller than in the larger rats, which fact agrees very well with the law formulated by Jackson (1909): "A relatively large embryonic head is characteristic of vertebrates in general." The head in the smaller prenatal controls also has a higher relative percentage weight than in the normal newborns, the difference decreasing with the increase in the weight of the prenata controls.

In my test rats the average weight of the head forms 24.0 per cent, 24.1 per cent, 23.5 per cent, 22.3 per cent, and 22.0 per cent of the body-weight from Group 1 to Group 5, respectively (computed from Table 5). Therefore, the relative weight of the head is slightly higher in the test rat than in the prenatal controls, except in Group 1.

The absolute weight of the head in the test rats exceeds that of the corresponding prenatal controls by 2.8 per cent, 6.0 per cent, 3.8 per cent, 6.5 per cent, and 7.6 per cent in Groups 1, 2, 3, 4 and 5, respectively, averaging 5.3 per cent above in the test rats. Thus in prenatal inanition the head shows a slight increase in weight, which is due partly to the increase in weight of the brain, eyeballs, and the integument covering the head.

In postnatal inanition in young rats, a stronger tendency for the head to increase in weight, even when the body-weight has been held constant, has been noted (Table 6). Stewart (1918*a*) found the head to increase 45 per cent in weight (as compared with controls of the same body-weight) in rats held at a constant body-weight from birth to sixteen days. In a series of rats stunted by underfeeding from birth to three weeks (body-weight 10 gm.) the average increase in the weight of the head was 16 per cent, as compared with controls of the same body-weight. In rats underfed from the age of three weeks to ten weeks, there was an apparent increase in head-weight of 2.1 per cent as compared with controls of the same body-weight (Jackson,[19] 1915). This slight gain in weight is attributed to the slight gain in skeletal weight, which in the head probably overbalances the loss in weight of the integument.

In both acute and chronic inanition in adult rats, the head increases markedly in relative weight and loses slightly in absolute weight (Jackson,[18] 1915).

From the foregoing it appears that the head manifests its strongest relative growth tendency in rats underfed from birth to sixteen days. That this growth tendency, though apparently less intense, is present before birth is evidenced by the increase of the head-weight of the test rats as compared with prenatal controls of the same body-weight.

Extremities and trunk.—In my normal newborn series, the fore limbs form 7.0 per cent and the hind limbs 7.6 per cent of the body-weight, 4.92 gm. This is a lower relative weight than given by Jackson and Lowrey (1912) for the relative weight of the extremities in the newborn rat of 5.3 gm., their figures being 7.39 per cent and 9.45 per cent for the fore and hind limbs, respectively. This difference is probably due to a variation in technic. Although the fore and hind limbs were always severed from the body at the shoulder and hip joints, respectively, it was extremely difficult to leave the same amount of skin and muscle attached to the limb in each case.

In my prenatal controls, the fore limbs form 5.3 per cent, 6.8 per cent, 7.4 per cent, 6.7 per cent, and 7.1 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the fore limbs in the smaller prenatal control fetuses is less than in the normal newborn, but this difference, in relative weight, decreases with the increase in the size of the fetus.

In the test rats, the fore limbs form 6.8 per cent, 6.8 per cent, 7.2 per cent, 7.3 per cent and 7.1 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, with the exception of Group 1, in which the relative weight of the fore limbs in the tests quite markedly exceeds that of the prenatal controls, there is very little difference in the relative weights in the fore limbs of the test rats and prenatal controls, in both of which the fore limbs form a relatively smaller percentage of the body-weight, especially in the smaller rats, than in the normal newborn.

The absolute weight of the fore limbs in the test rats in Group 1 exceeds that of the prenatal controls by 34 per cent (Table 5). In the other groups, however, the difference between the absolute weights of the fore limbs of the test rats and prenatal controls is so irregular that it would be extremely hazardous to draw any conclusions, the average in the test rats being 8 per cent above that of the prenatal controls.

The hind limbs in my prenatal controls form 5.2 per cent, 6.3 per cent, 6.8 per cent, 7.0 per cent, and 7.0 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore, as compared with the normal newborn, the hind limbs in the prenatal controls (fetuses) have a lower relative weight, and as in the case of the fore limbs, this difference in relative weight is most marked in the smaller rats (fetuses) and decreases with the increase in size of the prenatal control (fetus).

In my test rats the hind limbs form 6.7 per cent, 7.5 per cent, 7.4 per cent, 7.9 per cent, and 7.9 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore, in the test rats, the hind limbs form a higher relative percentage of the body-weight than in the prenatal controls. It thus appears that in the test rats the hind limbs are growing faster than the body as a whole.

The absolute weight of the hind limbs in my test rats exceeds that of the prenatal controls in all the groups, being 36.4 per cent, 19.5 per cent, 9 per cent, 13 per cent, and 20 per cent above in Groups, 1, 2, 3, 4 and 5, respectively (Table 5), the average being 19.5 per cent.

It is to be noted that in the prenatal controls the hind limbs, as compared with the fore limbs, have a lower or just equal weight, and the earlier in pregnancy the fetus is removed from the mother the larger are the fore limbs as compared with the hind limbs. This is in accord with the law of cranio-caudal progression in growth as formulated by Jackson (1909). This also may explain the larger size of the hind limbs in the test rats, since in the prenatal controls this growth tendency in the hind limbs has not had sufficient time to develop, due to their shorter sojourn *in utero*, as compared with the test rats, which, although undersized, were born at term.

Jackson and Lowrey (1912), in newborn rats, found the weight of the trunk to be 3.36 gm. In my newborns, the trunk weighs 3.16 gm. and forms 64.4 per cent of the average body-weight, 4.92 gm. In my prenatal controls the trunk forms 65.2 per cent, 64.0 per cent, 63.4 per cent, 65.4 per cent, and 65.3 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the trunk in the prenatal controls is smaller than in the newborn rats. In my test rats the trunk forms 62.7 per cent, 62.3 per cent, 62.3 per cent, 65.5 per cent, and 63.3 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5).

Thus in the test rat the trunk has about the same relative weight as in the newborn rat, while the relative weight is slightly higher in the prenatal controls corresponding to the smaller size of their heads and extremities. The difference in the size of the trunk, however, is slight, as evidenced by the fact that its absolute weight in the test rats shows an average loss of but 1.6 per cent. This loss of weight in the trunk compensates for the larger head and extremities in the tests.

Consequently it appears that in prenatal retardation by inanition there is a slight increase in the weight of the fore limbs especially in the smaller rats, a more marked increase in the hind limbs, and a slight decrease in the weight of the trunk. In postnatal starvation in young rats held at a constant body-weight there was very little change in the weights of the trunk and extremities as compared with controls of the same body-weight. In general, there was a slight increase in the weight of the head, counterbalanced by a slight decrease in the weight of the trunk and extremities (Jackson,[19] 1915; Stewart, 1918). During inanition in adult rats, both the head and extremities appear to increase in relative weight, while the trunk decreases (Jackson,[18] 1915; Table 6).

Integument.—In my normal newborns the average weight of the integument is 0.794 gm. (16.1 per cent of body-weight, 4.92 gm.). Stewart (1919), in new-born litters from the same colony, found the weight of the integument to be 0.754 gm. (15 per cent of the body-weight, 5.03 gm.). These values are slightly lower than that given by Jackson and Lowrey (1912), which was 0.930 gm. (19.8 per cent of body-weight). The difference is probably due to a variation in technic, as it is difficult to remove the skin with uniformity.

In my prenatal controls the weight of the integument forms 11.0 per cent, 12.8 per cent, 13.4 per cent, 13.9 per cent, and 14.2 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the weight of the normal integument is relatively less in the fetus, increasing progressively up to birth.

In my test rats the weight of the integument forms 12.4 per cent, 13.6 per cent, 15.3 per cent, 15.3 per cent, and 14.5 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). The integument in the test rats thus forms a relatively higher percentage of the body-weight, in all the groups, than in the prenatal controls.

The absolute weight (Table 5) of the integument in the test rats exceeds that of the prenatal controls by 18 per cent in Group 1, 6.4 per cent in Group 2, 14.6 per cent in Group 3, 10 per cent in Group 4, and 3 per cent in Group 5. The average increase in all the groups is 10.4 per cent. Although this increase in weight is irregular, it has a downward trend from Group 1 to Group 5 and shows that the nearer the prenatal controls and test rats approach their normal birth-weight, the less is the difference in the relative percentage and absolute weights of their integuments. This increase may be due to the longer interval the test rats remained *in utero* as compared with the prenatal controls, or to the fact that the skin has a stronger growth tendency at this time as compared with some of the other parts of the body. It is interesting to note (Table 6) that Stewart (1918) found the integument to remain at a constant weight in rats starved from birth to three weeks of age, while in older rats starved for longer or shorter periods the loss in weight of the integument was quite marked. In a younger series kept at a maintenance diet from birth to eleven days to twenty-two days, Stewart (1919) found the absolute weight of the integument in the test rats to be 25 per cent above that in the controls of the same body-weight. Jackson[18] (1915) found the integument to lose weight in nearly the same proportion as the whole body in acute and chronic inanition in adult rats.

Skeleton.—As explained under the section on materials and methods, the "moist" skeleton probably corresponds closely to that referred to by Jackson [19](1915) as the cartilaginous skeleton. Since the "gold dust" solution used to rid the skeleton of its ligaments and periosteum acted too strongly on the skeleton in my very small rats, causing a disintegration of the cartilages, no attempts were made to obtain anything corresponding to the cartilaginous skeleton. My observations on the "dried skeleton" are consequently on the dried ligamentous skeleton. Jackson and Lowrey (1912) obtained a value of 0.810 gm. for the ligamentous skeleton in the newborn rats, while in my normal newborn the "moist" skeleton weighs but 0.381 gm., 7.8 per cent of the body-weight, 4.92 gm. However, this agrees very well with the weight of the newborn moist skeleton of 10.377 gm. or 9.0 per cent body-weight, 4.92 gm., given by Conrow (1915). It must be stated, however, that despite the greatest care taken in cleaning the skeletons, their range of weight was very great, even in rats of equal weights (Table 5).

In my prenatal controls, the weight of the moist skeleton forms 7.2 per cent, 7.2 per cent, 7.4 per cent, 7.1 per cent, and 6.7 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the moist skeleton in the prenatal controls has a relative weight slightly below that of the normal newborn rat.

In my test rats the weight of the moist skeleton forms 5.0 per cent, 7.0 per cent, 7.4 per cent, 7.2 per cent, and 7.0 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus there is very little difference in the relative weight of the moist skeleton in the test rats and prenatal controls, except in Group 1, where its relative weight in the test rats is considerably below that of the prenatal controls. This difference is probably due to errors in technic.

By comparing the absolute weights of the moist skeleton in the test rats with the prenatal controls in Table 5, it will be seen that in Group 1 the absolute weight of the moist skeleton in the test rats is 27 per cent less than in the prenatal controls of the same body-weight. Since such a marked difference can not be accounted for by any change in body-length, in fact, the average body-length of the test rats is 7.3 per cent greater than in the prenatal controls of this group, it must be attributed to errors in technic. In the other four groups the difference in the absolute weights of the moist skeleton in the test rats and prenatal controls is very slight and wholly within the limits of error, considering the difficulties of technic. Probably there is very little real difference between the absolute weight of the moist skeleton in test rats and prenatal controls, but one can hardly reach any definite conclusion.

It should be noted, however, that in postnatal inanition the skeleton (undried) shows its greatest increase in weight, 32 per cent, in rats underfed from the age of three weeks to one year (Stewart, 1918). In rats underfed from birth to sixteen days the gain in the skeleton, with musculature, is but 6 per cent (Stewart, 1919). This seems to show that the growth tendency in the skeleton is relatively weak at birth, which may explain its apparent loss of weight in my test rats.

In my normal newborn series the weight of the dried skeleton is 0.089 gm. or 1.8 per cent of the body-weight, 4.92 gm. Conrow (1915) found the dried skeleton to be 1.9 per cent of the body-weight in the normal newborn rat (body-weight, 4.2 gm.; calculated weight of dried skeleton, 0.081 gm.).

In my prenatal controls the weight of the dried skeleton forms 1.4 per cent, 1.5 per cent, 1.5 per cent, 1.7 per cent, and 1.6 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the dried skeleton in the prenatal control has a relative weight slightly below that of the normal newborn rat.

In my test rats the weight of the dried skeleton forms 1.5 per cent, 1.8 per cent, 1.7 per cent, 1.8 per cent, and 1.7 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the dried skeleton in the test rats is slightly higher than in the prenatal controls.

Concerning the absolute weight of the dried skeleton, however (Table 5), the results obtained are different from those in the case of the moist skeleton. Although in Groups 1, 2, and 3 (Table 5) the absolute weights of the moist skeletons in the test rats were 27 per cent, 1.8 per cent, and 5.0 per cent below the prenatal controls of the respective groups, and 0.4 per cent and 0.01 per cent above in Groups 4 and 5, respectively, the absolute weight for the dried skeleton of the test rats exceeds that of the prenatal controls in all five groups, the excess being 7 per cent, 20 per cent, 14 per cent, 9 per cent, and 9 per cent, respectively, from Groups 1 to 5 (Table 5), averaging 12 per cent above for all groups.

This increase in the weight of the dried skeleton in the test rats is evidently due to an increase of dry substance in the bones, cartilages, and ligaments. Therefore, since the dry skeleton shows a relatively greater increase in the test rats as compared with the prenatal controls of the same body-weight, it is apparent that, although the body-weight is retarded, the relative percentages of solid substance and water in the test rats tend to approach that found in the normal newborn rat. The tendency of the skeleton to grow in mass (although at a retarded rate) in cases of underfeeding in rats was observed by Jackson[19] (1915) and by Stewart (1918). Lowrey (1913) found that in the postnatal growth of the rat the amount of dry substance in the ligamentous skeleton increases with age, being 18.1 per cent at birth, 33.3 per cent at twenty days, 39.2 per cent at six weeks, 45.9 per cent at ten weeks, 50.4 per cent at five months, and 52.6 per cent at one year.

No observations were made on any of the skeletons to determine whether there was any variation in the normal process of differentiation (developmental changes) between the test rats and prenatal controls. Jackson[19] (1915) and Stewart (1918), however, found that during maintenance of body-weight by underfeeding in young rats, skeletal growth and differentiation occurred apparently in a normal manner, although at a retarded rate.

Musculature.—The musculature was not weighed separately, but was weighed together with the skeleton and its weight obtained by subtracting the latter from the combined weight. The weight given by Jackson and Lowrey (1912) for the newborn rat is 1.15 gm. or 24 per cent of body-weight, 5.3 gm.; while in my newborns the weight of the musculature was 1.77 gm. or 36 per cent of the body-weight, 4.92 gm. This marked difference is probably due to a variation in technic, as in all my rats the fat was included with the musculature. The reason for this difference in technic is obvious, because in the small rats the fat was poorly differentiated from the muscle.

In my prenatal controls the musculature forms 28 per cent, 32 per cent, 32 per cent, 36.5 per cent, and 37.5 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the prenatal controls it is evident that the relative weight of the musculature is less in the smaller rats, increasing progressively up to birth.

In my test rats the musculature forms 28 per cent, 30 per cent, 31 per cent, 33 per cent, and 34 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, in both the test rats and prenatal controls there is apparently an increasing tendency for the musculature to make up a larger proportion of the body weight as the rat increases in size; that is, the muscle is growing at a relatively faster rate than the remainder of the body, the increase being slightly more marked in the prenatal controls than in the test rats.

The absolute weight of the musculature in the test rats is slightly below that of the prenatal controls with the exception of Group 1 (Table 5), in which its absolute weight in the test rats is 7 per cent above that in the prenatal controls. Taking the groups as a whole, the absolute weight of the musculature in the test rats is but 5 per cent below that in the prenatal controls. This difference is slight, and may in part be due to a decrease in the fat in the test rats. On account of the difficulties encountered in separating the fat from the musculature, they were weighed together, as previously stated.

In postnatal inanition in young rats, there is apparently a slight gain in weight of the musculature. It shows an increase of but 6 per cent, 8 per cent, 10 per cent and 3 per cent, respectively, in rats underfed from birth to sixteen days, from birth to three weeks, from birth to ten weeks, and from three weeks to ten weeks of age (Stewart, 1918, 1919; Jackson,[19] 1915). The greatest gain observed (25 per cent) was in rats underfed from ten weeks to eight months of age (Jackson,[19] 1915). In both acute and chronic inanition in adult rats the musculature loses in about the same proportion as the body as a whole (Jackson, 1915).

In general, it appears that the musculature manifests a relatively weak growth tendency during both prenatal and postnatal inanition, with even a slight loss in the former.

Visceral group.—The visceral group includes the brain, spinal cord, eyeballs, and thyroid, as well as the abdominal and thoracic viscera. Jackson and Lowrey (1912) give the weight of the visceral group in the newborn as 0.954 gm. or 18 per cent of the body-weight, 5.3 gm. Stewart (1919) gives the visceral group a weight of 0.871 gm.; or 17.3 per cent of the body-weight, 5.03 gm. The visceral group in my normal newborn series weighs 0.817 gm. or 16.6 per cent of the body-weight, 4.92 gm.

In my prenatal controls the weight of the visceral group forms 23 per cent, 21 per cent, 18.5 per cent, 19.5 per cent, and 19 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore it is evident that the relative weight of the visceral group in the prenatal controls (fetuses) exceeds that of the normal newborn rat. This difference is most marked in the smaller rats (fetuses), decreasing as the birth-weight is approached, showing that in the fetal life of the rat (from 2 gm. to 4.1 gm.) the viscera constitute a larger proportion of the body-weight than at birth.

In my test rats the weight of the visceral group forms 16.2 per cent, 16.6 per cent, 16.6 per cent, 16.2 per cent, and 15.2 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, in the test rats the visceral group forms a slightly smaller percentage of the body-weight than in the normal newborn, while in the prenatal controls the converse is true. The relative weight of the visceral group is markedly lower in the test rats than in the prenatal controls.

In my test rats the absolute weight of the visceral group is less than that of the prenatal controls in all the groups (Table 5). In Groups 1 to 5 the absolute weight of the visceral group in the test rats is 27 per cent, 21 per cent, 7 per cent, 17 per cent, and 20 per cent below that of the prenatal controls in the corresponding groups, averaging 18.4 per cent below.

Thus in prenatal inanition the visceral group shows a marked retardation in growth. This is due chiefly to the retarded growth of the liver and lungs.

These results are directly opposed to those in postnatal inanition shortly after birth. Stewart (1918, 1919) found that the absolute weight of the visceral group exceeded that of controls of the same body by 46 per cent, 28 per cent, and 38 per cent in rats underfed from birth to an average of sixteen days, from birth to three weeks of age, and from birth to ten weeks of age, respectively (Table 6). In rats underfed from the age of three weeks to ten weeks and from the age of three weeks to one year, there was no marked change in the weight of the visceral group (Jackson,[19] 1915; Stewart, 1918); while in rats underfed from ten weeks of age to eight months, Jackson[19] (1915) found the weight of the visceral group to be 12 per cent below the normal. He found that the visceral group as a whole undergoes very little change in relative weight in adult rats during either acute or chronic inanition.

From the foregoing data it is evident that the growth tendency of the visceral group in the rat during inanition is relatively weak before birth, strongest shortly after birth, and decreases gradually thereafter.

Remainder.—The "remainder" is obtained by subtracting the weight of the integument, "moist" skeleton, musculature, and viscera from the net body-weight. It thus includes the loss by evaporation of fluids which escape from the body during dissection, also the larynx, trachea, esophagus, salivary and lymph glands, large vessels, and pieces of fat in the omentum. The remainder may vary with the amount of fat removed from different portions of the body.

In general, no attempt was made to remove any of the fat, such as the "nuchal fat pad," retroperitoneal fat, and so forth, all of which was included in the musculature.

In my normal newborns (body-weight 4.92 gm.) the average weight of the remainder was 1.05 gm. (21 per cent of body-weight) Stewart (1919) found its weight to be 1.52 gm. (30 per cent of net body-weight, 5.03 gm.). This weight is considerably higher than mine, probably due to the fact that he included more fat with the remainder than with the musculature. Jackson and Lowrey (1912), however, found its weight to be 0.97 gm. (20.56 per cent of body-weight, 5.3 gm.), a value very close to mine.

In my prenatal controls the weight of the remainder forms 31 per cent, 27 per cent, 28 per cent, 23 per cent, and 23 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the remainder in the smaller prenatal control rats (fetuses) markedly exceeds that of the normal newborn rat, the difference decreasing as the normal birth-weight is approached.

In my test rats the weight of the remainder forms 37 per cent, 34 per cent, 31 per cent, 28 per cent and 30 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore the relative weight of the remainder in the test rats exceeds that of the prenatal controls in all the groups.

The absolute weight of the remainder in my test rats was considerably above that of my prenatal controls in all the groups, the average being 25.4 per cent above (Table 5).

This relative and absolute increase in the remainder is directly opposed to the results obtained in investigations on postnatal starvation (Table 6). In rats held at a constant weight from birth to sixteen days, in another group underfed from birth to three weeks (body-weight 10 gm.), and in another series underfed from birth to ten weeks, Stewart (1918, 1919) found in the remainder a decrease of 59 per cent, 40 per cent, and 23 per cent, respectively, as compared with normal controls of the same body-weight. In rats underfed from the age of three weeks to ten weeks, however, Jackson[19] (1915) found but 2 per cent decrease in the remainder. In young rats underfed up to one year of age he found a decrease of but 5 per cent, while in Stewart's series (1918) there is a decrease of 33 per cent. In acute and chronic inanition in adult rats there is a definite decrease in the weight of the remainder, probably due to a loss of fat (Jackson,[18] 1915).

Why the remainder should decrease during postnatal starvation and increase during prenatal inanition is difficult to explain. Possibly there is a larger amount of circulating fluids, blood, lymph, and so forth, in my test rats than in the prenatal controls. This increase in the remainder evidently compensates for the loss in weight of the visceral group. This is the converse of what occurs in postnatal starvation, as found by Stewart (1919) in the rats held at birth-weight.

Brain.—In my normal newborns the average weight of the brain is 0.235 gm., (4.8 per cent of the body-weight, 4.92 gm.). Stewart (1919) gives the weight of the brain in the newborn as 0.224 gm. (4.5 per cent of the body-weight, 5.03 gm.). Jackson (1913) found the weight of the brain in the newborn rat to be 4.8 per cent of the gross body-weight.

In my prenatal controls the weight of the brain forms 6.2 per cent, 5.6 per cent, 5.0 per cent, 4.8 per cent, and 4.4 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the prenatal controls the relative weight of the brain in the smaller rats (fetuses) is greater than that of the normal newborn, this difference in relative weight decreasing, however, as the birth-weight is approached.

In my test rats the weight of the brain forms 6.6 per cent, 6.2 per cent, 5.6 per cent, 5.3 per cent and 5.0 per cent of the body-weight in

Groups 1 to 5, respectively (computed from Table 5). Thus, in the test rats the brain forms a slightly higher per cent of the body-weight than in the prenatal controls; in both, the smaller the rat, the greater is the weight of the brain relative to the body-weight. Since in the test rats, especially in the smaller ones, the brain tends to form a relatively larger part of the body-weight than in either the normal newborns or in the prenatal controls, it may be quite safely assumed that in a state of inanition of the mother the brain of the fetus has a greater growth tendency than does the remainder of the body as a whole.

In the test rats the absolute weight of the brain exceeds by 12 per cent to 13 per cent (average 12.5 per cent) that in the corresponding prenatal norms, constantly throughout all the groups (Table 5).

Comparing these results with those obtained in postnatal inanition by Jackson and Stewart (Table 6), it is seen that the brain shows its greatest tendency to increase in weight in rats underfed from birth to sixteen days (Stewart, 1919). Here the brain shows a gain of 125 per cent in absolute weight above controls of the same body-weight. This gain drops to 60 per cent in rats (body-weight 10 gm.) underfed from birth to three weeks (Stewart, 1918); and in rats starved from birth to ten weeks the gain is but 8 per cent. In rats underfed from three weeks after birth to ten weeks of age the brain shows little or no change (Jackson,[19] 1915).

Hatai (1904) found a decrease of 5 per cent in the absolute weight of the brain in young rats losing 30 per cent of their body-weight on an unfavorable diet of starch and beef fat. Later (1908) he found no change in the brain-weight in rats stunted on an unfavorable diet, as compared with normal rats of the same body-weight.

Donaldson (1911), in young rats held at maintenance from thirty days to fifty-one days of age, found the brain-weight to average 7 per cent less than in normal controls of the same age. If a comparison is made, however, with the calculated initial brain-weight, as he points out, the average weight of the brain is 3.6 per cent greater in the underfed rats.

In adult rats, during both acute and chronic inanition, Jackson[18] (1915) observed that the brain even loses slightly in weight.

From the foregoing results, it may be assumed that in the rat during inanition the brain possesses its strongest growth tendency at birth and that this tendency decreases with age (Table 6). Whether this growth impulse is stronger or weaker before birth is hard to decide. From a comparison of the data it would seem to be weaker before birth, since in my test rats from underfed mothers the weight of the absolute brain increased but 12.5 per cent above that of the prenatal norms, while Stewart (1918*a*), in starvation seventeen days to twenty-two days after birth, found the absolute weight of the brain to gain 125 per cent above that of the controls of the same body-weight. It must be remarked, however, that in my tests the exact character and extent of the inanition of the fetus are somewhat uncertain.

Spinal cord.—In my normal newborns the spinal cord weighs 0.036 gm. (0.71 per cent of the body-weight, 4.92 gm.). Stewart (1919) gives the weight of the spinal cord in the newborn as 0.035 gm. (0.70 per cent of the body-weight, 5.0 gm.). The Wistar norm (Donaldson, 1915) for the spinal-cord weight is 0.034 gm. at body-weight of 4.95 gm.

The weight of the spinal cord in my prenatal controls forms 1.12, per cent, 1.00 per cent, 0.91 per cent, 0.83 per cent, and 0.75 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the spinal cord, similar to the brain, in the prenatal controls has a higher relative weight than in the normal newborn rat.

In my test rats the weight of the spinal cord forms 1.13 per cent, 1.01 per cent, 0.86 per cent, 0.80 per cent, and 0.75 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5).

Thus, in the smaller rats, both the test rats and prenatal controls, as compared to the normal newborns, the spinal cord forms a relatively higher percentage of the body-weight, this tendency lessening with the increase in the size of the rats, until in the larger rats this difference in relative weight disappears.

From the data in Table 5, the absolute weight of the spinal cord is lower in the test rats than in the prenatal controls, with the exception of Groups 1 and 2, where it is respectively 6 per cent and 2 per cent higher in the test rats. The absolute weight in all the groups averages but 0.26 per cent higher in the prenatal controls than in the test rats. This is such a slight difference that it might very well be attributed to errors in technic, since it is difficult to remove the cord intact from these small rats and also to sever the head from the trunk at exactly the same place. Probably there is very little change in the spinal cord of the fetus during inanition in the mother. The fact that the body-length in the tests and controls varies but little, 1 per cent higher in the test rats, would lead one to expect but little difference in the corresponding weights of the spinal cord.

The results obtained in postnatal inanition, however, might lead one to expect an increase in the size of the cord in the stunted individual. Bechterew (1895), in acute inanition of puppies and kittens, made a study of the central nervous system after death of the animal and found the least loss in the spinal cord. Donaldson (1911) found a slight increase in the weight of the spinal cord in young rats, held at body-weight of 34 gm. from thirty days to fifty-one days of age. Jackson (1915) found no change in the weight of the spinal cord in acute inanition in adult rats, while in chronic inanition in adult rats he found a slight decrease in the weight.

In newborn rats, however, Stewart (1919) noted a marked tendency for the cord to continue growing during inanition in which the body is kept at nearly constant weight. From the data in Table 6, it is evident in underfed young rats that the spinal cord possesses a very strong growth tendency, greatest at or shortly after birth, but also present up to adult life. It should be noted that this growth tendency persists for a longer time in the cord than in the brain, probably due to the fact that the brain normally completes its postnatal growth at a relatively earlier age than does the cord.

Why the cord should lose while the brain gains in weight during fetal inanition is difficult to explain. So far as their normal growth tendency during the fetal period is concerned, both appear to be decreasing in about the same relative proportion, judging from a comparison of their prenatal growth norms.

Eyeballs.—The eyeballs in my normal newborns weigh 0.025 gm. and form 0.50 per cent of the body-weight, 4.92 gm. In Stewart's (1919) newborn they weighed 0.0235 gm. and formed 0.47 per cent of the body-weight, 5.03 gm. Jackson (1913) gives the weight of the eyeballs in the newborn as 0.025 gm. and 0.53 per cent of the body-weight.

In my prenatal controls the eyeballs form 0.38 per cent, 0.42 per cent, 0.42 per cent, 0.38 per cent, and 0.37 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Compared with the normal newborn rat, the relative weight of the eyeballs is much lower in the prenatal controls.

In my test rats the eyeballs form 0.57 per cent, 0.52 per cent, 500. per cent, 0.48 per cent, and 0.46 per cent of the body-weight in

Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the eyeballs in the test rats have a much higher relative weight than in the prenatal controls. In the test rats the relative weight of the eyeballs is about the same as that of the normal newborn. (In the smaller rats it is slightly higher.)

The absolute weight of the eyeballs is markedly higher in the test rats than in the controls in all the groups (Table 5), being most pronounced in Group 1 (the smallest rats), in which the average absolute weight of the eyeballs of the test rats is 56 per cent above that in the prenatal controls. It is interesting to note that, in the range of their weights, in Group 1 the heaviest eyeballs in the prenatal control just equal the lightest in the test rats. In the other groups the eyeballs in the test rats show an increase in absolute weight above the prenatal controls of over 20 per cent. The average total excess of the absolute weight of the eyeballs in the test rats above that in the prenatal controls is 31.4 per cent.

These results are quite in accord with those obtained in postnatal inanition, although less marked. In postnatal inanition the strongest growth capacity of the eyeball is exhibited in newborns underfed from birth to an average of sixteen days (Stewart, 1919), the increase being 146 per cent (Table 6). This growth capacity of the eyeball during inanition then decreases somewhat, but rises again in older rats and persists in animals underfed up to one year of age. In older rats (adults), in both acute and chronic inanition, the eyeballs lose slightly in weight according to Jackson (1915). He suggests that this remarkable capacity of the eyeball to continue its growth during inanition may be due to its power to absorb water, which makes up so large a proportion of its composition.

Thymus.—In my normal newborns, the average weight of the thymus is 0.0070 gm. or 0.14 per cent of the body-weight, 4.92 gm. Stewart (1919) gives the weight of the thymus in the newborn as 0.0079 gm. or 0.15 per cent of the body-weight—5.03 gm. The Wistar norm (Donaldson, 1915) is 0.0080 gm., body-weight, 4.9 gm.

In my prenatal controls the thymus forms 0.11 per cent, 0.13 per cent, 0.13 per cent, 0.13 per cent, and 0.12 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the thymus in the prenatal controls is slightly lower than in the normal newborn rat.

In my test rats the thymus forms 0.08 per cent, 0.09 per cent, 0.11 per cent, 0.11 per cent, and 0.10 per cent of the body weight in Groups 1 to 5, respectively (computed from Table 5). Thus the thymus forms a much smaller part of the body-weight in the test rats than in the prenatal controls; that is, its growth has been retarded in the test rats. This is more clearly brought out by a comparison of the absolute weights. In Group 1 the absolute weight of the thymus, in the test rats, is 29 per cent below that of the prenatal controls; in Group 2, 33 per cent below; in Group 3, 12 per cent below; in Group 4, 16 per cent below; and, in Group 5, 15 per cent below, averaging 21 per cent below for all groups. Thus it is seen that the growth of the thymus is considerably retarded in the rat fetus during inanition of the mother.

These results also agree with the loss of weight (hunger involution) of the thymus in cases of postnatal inanition. Jonson (1909), in young rabbits, kept at constant body-weight by underfeeding for four weeks, found the weight of the thymus to be reduced to one-thirtieth of that in the controls, the greatest loss of weight being in the cortex. He also found that the reduction in weight of the thymus was proportionate to the loss of the body-fat. This reduction in weight of the thymus in rabbits is much more marked than that obtained by Jackson and Stewart on rats. Jackson[19] (1915) found a loss of 90 per cent in the thymus in young rats held at maintenance from the age of three weeks to ten weeks and also in young rats underfed ten weeks to eight months. Stewart (1918 and 1919) found losses of 80 per cent, 30 per cent, and 49 per cent, respectively, in the weights of the thymus in young rats underfed from birth to ten weeks, from birth to three weeks, and held at birth-weight for sixteen days. Jackson[18] (1915) found no marked change in the weight of the thymus in cases of acute and chronic inanition in adult rats, at which age involution of the thymus had already occurred. The thymus normally reaches its maximum absolute weight in the rat at eighty-five days (Hatai, 1914) and at one year it has undergone a complete age involution (Jackson, 1913).

Heart.—In my normal newborns, the average weight of the heart is 0.027 gm. or 0.55 per cent of the body-weight, 4.92 gm. Jackson (1913) gives its weight in the newborn as 0.030 gm. or 0.65 per cent of the body-weight, 5.08 gm. Stewart (1918*a*) gives a weight of 0.031 gm., or 0.61 per cent of the body-weight, 5.03 gm.

In my prenatal controls the weight of the heart forms 0.49 per cent, 0.52 per cent, 0.49 per cent, 0.50 per cent, and 0.44 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the heart in the prenatal controls is considerably less than in the normal newborn rat.

In my test rats the weight of the heart forms 0.55 per cent, 0.53 per cent, 0.54 per cent, 0.53 per cent and 0.49 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the heart in the test rats is slightly higher than in the prenatal controls. The relative weight in both the test rats and prenatal controls is less than that in the normal newborn rats. It is also evident that in both the prenatal controls and test rats the relative weight of the heart is greater in the smaller as compared with the larger rats.

The absolute weight of the heart is constantly higher in the test rats than in the prenatal controls, the difference being most marked in Group 1 (Table 5) in which the heart weight in the test is 17 per cent higher than that in the prenatal controls. This difference, however, is not so pronounced in the other groups, averaging for all groups 8 per cent above in the test rats.

This gain in heart-weight in prenatal starvation agrees with the results of Stewart (1919), who noted a gain of 26 per cent in absolute weight of the heart in test rats kept at a birth-weight of about 5 gm. for an average of sixteen days. However, in another series (Stewart, 1918) starved from birth to three weeks (body-weight 10 gm.), the heart showed a loss of 5 per cent. In still another group, underfed from birth to ten weeks (body-weight 24 gm.), Stewart (1918) found a gain of 27 per cent in the weight of the heart. In slightly older rats, underfed for various periods, the heart loses slightly (Jackson,[19] 1915; Stewart, 1918), while in adult rats the heart shows a decided loss in both acute and chronic inanition (Jackson, 1915).

Lungs.—Jackson (1913) gives the absolute weight of the lungs as 0.078 gm. or 1.6 per cent of the body-weight, 5.1 gm. The Wistar norm (Donaldson, 1915) is 0.079 gm., or 1.6 per cent of the body-weight, 4.9 gm. In my newborn controls the weight of the lungs is 0.073 gm., or 1.5 per cent of the body-weight, 4.92 gm.

In my prenatal controls the lungs form 2.8 per cent, 2.7 per cent, 2.3 per cent, 2.0 per cent and 2.1 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the lungs is markedly higher in the prenatal controls than in the normal newborn rats. This difference in relative weight is greatest in the smaller rats and decreases as the birth-weight is approached.

In my test rats the lungs form 1.2 per cent, 1.5 per cent, 1.4 per cent, 1.5 per cent and 1.3 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, in the test rats the lungs have a relative weight which is about that of the normal newborn rat, whereas in the prenatal controls the relative weight is approximately double that at birth.

The absolute weight of the lungs in the test rats is 54 per cent, 44 per cent, 40 per cent, 23 per cent and 36 per cent below that of the prenatal controls in Groups 1 to 5, respectively, averaging 39.4 per cent below for all groups. It is interesting to note that in the range of the individual weights the largest lungs in the test rats about equal in size the smallest in the controls.

This lack of ability of the lungs to grow, manifested by a subnormal weight during prenatal inanition, agrees with the results obtained in the postnatal starvation experiments (Table 6). Stewart (1919) found a slight gain (3 per cent) in the lungs of rats underfed from birth to an average of sixteen days. On underfeeding from birth to three weeks, and from birth to ten weeks of age, the lungs showed a loss of 26 per cent in both series (Stewart, 1918). Jackson[19] (1915) found that the lungs lose 15 per cent in rats starved from the age of three weeks to ten weeks. He also found a loss of 13 per cent in the lungs in a group underfed between the ages of ten weeks and eight months. Stewart (1918), however, found the lungs in rats underfed from an age of three weeks to one year to gain in weight 28 per cent (probably pathologic). Jackson[18] (1915) found that the lungs show a tendency to lose weight in adult rats in both acute and chronic inanition and that this loss of weight is about in proportion to the loss of the body as a whole. Consequently, it may be concluded that the lungs exhibit a very weak growth tendency during prenatal as well as during postnatal conditions of inanition.

Liver.—The Wistar norm (Donaldson, 1915) for the liver of the newborn rat is 0.205 gm., with a body-weight of 4.9 gm. Stewart (1919) gives the weight as 0.245 gm. or 4.9 per cent of the body-weight, 5.03 gm. Jackson (1913) finds a weight of 0.230 gm. or 4.3 per cent of the body-weight. In my newborns the weight of the liver is 0.250 gm. or 5.1 per cent of the body-weight, 4.92 gm.

In my prenatal controls the liver forms 9.1 per cent, 8.7 per cent, 7.8 per cent, 8.1 per cent and 7.7 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the liver in the prenatal controls markedly exceeds that of the normal newborn rat. This difference in relative weight decreases, however, as the normal birth-weight is approached.

In my test rats the liver forms 4.1 per cent, 4.5 per cent, 4.6 per cent, 4.9 per cent, and 4.4 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). In the smaller test rats, the liver forms a relatively smaller precentage of the body-weight than in the normal newborns. In the prenantal controls, however, the liver forms a much higher relative percentage of the body-weight than in either the normal newborns or in the test rats.

In the test rats the absolute weight of the liver is markedly subnormal in all the groups (Table 5), averaging 45 per cent below that of the prenatal controls In the range of the individual weights in the same groups the highest weight for the liver in the test rats is much below the lowest weight in the prenatal control. Thus in prenatal inanition the growth of the liver is markedly retarded, reaching an absolute weight of approximately one-half that of the prenatal controls.

In postnatal inanition, Stewart (1919) found that the liver loses 23 per cent in rats held at a constant weight from birth to an average of sixteen days (Table 6). In two other groups underfed from birth to three weeks, and from birth to ten weeks, he found that the liver gains in weight 17 per cent and 64 per cent, respectively. Jackson[19] (1915), in young rats underfed from the age of three weeks to ten weeks, found a gain of 10 per cent in the liver-weight. In rats starved for a longer period, or where it was begun later, the liver shows a loss of weight (Jackson,[19] 1915; Stewart, 1918). Jackson[18] (1915) found that the liver loses markedly in cases of acute and chronic inanition in adult rats.

Thus it would seem that in prenatal life and for a period up to several days after birth, the liver during inanition has a very weak growth tendency, which becomes stronger after the first week of postnatal life and persists up to six weeks or two months of age, then decreases until it is very weak again as the adult stage is approached.

Spleen.—The Wistar norm (Donaldson, 1915) for the spleen in the newborn rat is 0.008 for a body-weight of 4.9 gm. Jackson (1913) gives the weight of the spleen as 0.010 gm., or 0.22 per cent of the body-weight. Stewart (1919) finds the weight to be 0.011 gm., or

0.22 per cent of the body-weight, 5.03 gm. In my normal newborns the average weight of the spleen is 0.010 gm., or 0.20 per cent of the body-weight, 4.92 gm.

The spleen in the prenatal controls forms 0.08 per cent, 0.08 per cent, 0.13 per cent, 0.14 per cent, and 0.15 per cent of the body-weight in Groups 1 to 5, respectively, while in the test rats in the corresponding groups it forms 0.12 per cent, 0.12 per cent, 0.16 per cent, 0.17 per cent, and 0.21 per cent of the body-weight (computed from Table 5). Thus the spleen in the prenatal controls forms a much smaller proportion of the body-weight than it does in the normal newborn; that is, in the rat fetus the spleen is at first relatively small (0.08 per cent of body-weight in a 2.19-gm. fetus), but gradually increases in size up to shortly before birth (0.15 per cent of the body weight in a 4.19-gm. fetus), when, in order to reach its normal relative percentage of the newborn body-weight, it must increase rapidly in size (an increase from 0.15 per cent to 0.22 per cent of the body-weight while the fetus is growing from 4.19 gm. to 5.0 gm.).

Jackson (1909) in referring to the human fetus says:

> "The spleen is at first relatively small, but increases slowly to an average of 0.176 per cent of the whole body in the seventh month. About this time it appears to increase rapidly in relative size, averaging over 0.4 per cent in the eighth and ninth months. In the full-term still-born (143 cases) the spleen averages 0.32 per cent of the total body-weight, and in the live-born (101 cases) 0.43 per cent."

Lowrey (1911) finds practically the same course of growth in the spleen of the pig fetus.

Thus it appears that the prenatal growth of the spleen in the rat is similar to that observed in the human and the pig. In all three animals the spleen apparently develops a strong growth tendency shortly before birth. This probably explains the increase in the relative weight of the spleen in the test rats. Since the test rats have a longer time in the uterus, this late growth tendency in the spleen has more opportunity to develop than in the prenatal controls.

The absolute weight of the spleen in the test rats is constantly higher than that in the prenatal controls in all the groups (Table 5), averaging 34 per cent above.

This growth of the spleen during prenatal inanition agrees very well with the results obtained during postnatal starvation. Stewart (1919) found the spleen to gain 38 per cent in rats kept at birth-weight for an average of sixteen days of age. In another series (Stewart,

1918) underfed from birth to three weeks of age, the spleen lost 49 per cent. In a third series, starved from birth to ten weeks of age, the spleen gained 24 per cent. Jackson[19] (1915) found the spleen to lose 42 per cent in rats starved from three weeks of age to ten weeks. In two series starved during later periods (Jackson,[19] 1915; Stewart, 1918) there was no material change in its weight.

In adult rats in chronic inanition the reduction in the weight of the spleen is about the same as that for the whole body, while in acute inanition the loss is much greater (Jackson,[18] 1915).

Intestines.—The intestines, with their contents, have an average weight of 0.141 gm. and form 3.0 per cent of the body-weight (4.92 gm.) in my normal newborns. The empty intestines have an average weight of 0.062 gm. or 1.3 per cent of the body-weight.

In my prenatal controls the intestines with contents form 1.6 per cent, 1.9 per cent, 1.9 per cent, 2.4 per cent, and 2.3 per cent of the body-weight (computed from Table 5). Thus the relative weight of the intestines with contents is considerably less in the prenatal controls than in the normal newborn rat, the difference decreasing, however, as the prenatal control fetuses approach their birth-weight.

In my test rats the intestines with contents form 1.8 per cent 2.2 per cent, 2.5 per cent, 2.4 per cent, and 2.4 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the intestines with contents is slightly higher in the test rats than in the prenatal controls.

The empty intestines in my prenatal controls form 0.64 per cent, 0.75 per cent, 0.76 per cent, 0.93 per cent, and 1.60 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the relative weight of the empty intestines is lower in the fetus, increasing progressively up to birth.

In my test rats the empty intestines form 0.60 per cent, 0.71 per cent, 0.95 per cent, 0.82 per cent, and 0.90 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore the relative weight of the empty intestines in the test rats is slightly less than that of the prenatal controls.

The absolute weight of the intestines with contents, in the test rats, exceeds that of the prenatal controls in Groups 1, 2, 3, and 5 by 24 per cent, 17 per cent, 31 per cent, and 2 per cent, respectively. In Group 4 the absolute weight is 0.06 per cent lower in the test rats. From the foregoing it is evident that the intestinal contents in the smaller test rats markedly exceeds that of the smaller prenatal controls (fetuses), this difference disappearing in the larger rats, that is, as the normal birth-weight is approached.

The absolute weight of the empty intestines, however, in the test rats of Groups 1 and 2 is below that of the prenatal controls, 3 per cent and 5 per cent, respectively. In Group 3 in the test rats it is 27 per cent above, and in Groups 4 and 5 it is 12 per cent and 16 per cent respectively below that of the controls; averaging 2 per cent below in the test rats for all groups. This difference in absolute weight is slight and may be due to the difficulty of removing the intestinal contents in a uniform manner. It is difficult to explain on any other premises why the absolute weight of the intestines with contents in the test rats should exceed that of the controls by 15 per cent while below them 2 per cent in absolute weight when empty. Jackson[19] (1915), however, in underfed young rats, found an increase in the intestinal contents, while the empty intestines lost in weight. Since the full stomach in my test rats weighs 3.7 per cent less than that of the prenatal controls, there may be a passage of stomach contents into the intestines, with a possible increase of meconium and mucus in the older rats (test), which may account for the increase in the absolute weight of the full intestines in the test rats.

There may be a retardation of the growth of the intestines during prenatal inanition while the stomach increases slightly in weight. However, on account of the irregularities of the results obtained, it would be hazardous to venture any definite conclusion.

It has been found, however, that in postnatal inanition the gastro-intestinal tract taken as a whole manifests a marked growth capacity in rats starved shortly after birth. Stewart (1919) found that the intestines gained 40 per cent in weight in rats kept at a constant birth-weight for an average of sixteen days. In two other groups, underfed from birth to three weeks of age and from birth to ten weeks of age, Stewart (1918) found that the gastro-intestinal tract gained 17 per cent, and 100 per cent, respectively.

Jackson[19] (1915) also found that the gastro-intestinal tract gained 28 per cent in rats underfed from the age of three weeks to ten weeks. However, in cases of chronic inanition in rats underfed from the age of three weeks to one year (Stewart, 1918) and from the age of ten weeks to eight months (Jackson[19], 1915), there is a loss in the gastro-intestinal tract of 27 per cent and 26 per cent, respectively.

In adult rats, during both acute and chronic inanition, there is a marked decrease in the gastro-intestinal tract, both filled and empty, the loss being about 57 per cent in each group (Jackson,[18] 1915).

Stomach.—As described under the section on materials and methods, the stomach in the test rats and controls was weighed as a separate organ, instead of being included with the intestines and pancreas as the gastro-intestinal group. However, the stomach and intestines were removed and weighed full, and empty, in a group of four normal newborn rats (average body-weight 5.0 gm.). The average weight of the stomach and intestines with their contents was 0.317 gm. Their weight, empty, was 0.128 gm., a value which agrees very well with that of Jackson (1913), who gives their weights with and without contents as 0.297 gm. and 0.117 gm. respectively.

The full stomach in my normal newborns had an average weight of 0.1198 gm. (2.4 per cent of body-weight 4.92 gm.). The empty stomach weighed 0.020 gm. or 0.41 per cent of the body-weight. Hatai (1918) gives the weight of the empty stomach as 0.030 gm. or 0.70 per cent of the body-weight, 4.2 gm. This value is considerably higher than mine, probably due to a variation in technic.

In my prenatal controls, the full stomach forms 0.7 per cent, 1.5 per cent, 1.5 per cent, 1.2 per cent, and 1.8 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the full stomach in the prenatal controls is much less than that in the normal newborn rat. The small relative weight of the full stomach in Group 1 agrees with the observations of Jackson (1909) that in the human fetus the relative weight of the stomach with contents is at first but little larger than that for the empty stomach.

The full stomach in my test rats forms 1.9 per cent, 1.5 per cent, 1.5 per cent, 1.3 per cent, and 1.0 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the full stomach is greater in the smaller test rats, while the converse is true of the prenatal controls.

The absolute weight of the full stomach is variable, averaging 3.7 per cent less in the test rats than in prenatal controls (Table 5).

The empty stomach in my prenatal controls forms 0.31 per cent, 0.37 per cent, 0.39 per cent, 0.37 per cent, and 0.38 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the empty stomach in the prenatal controls is slightly less than that of the normal newborn rat, the difference in relative weight being most marked in Group 1.

In my test rats the empty stomach forms 0.34, per cent, 0.38 per cent, 0.40 per cent, 0.38 per cent, and 0.39 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, with the exception of Group 1, there is very little difference in the relative weight of the stomach in the test rats and in the prenatal controls.

In the largest rats (Group 5) the stomachs, in both the test rats and prenatal controls, has practically the same relative weight as in the normal newborn rats. Thus the normal relative weight of the stomach is disturbed very little by prenatal inanition. The stomach in the test rats shows an average of 5.6 per cent in absolute weight above the prenatal norms. The difference is most marked in Group 1 (the smallest rats), where the absolute weight in the test rats is 15 per cent above that of the controls (Table 5).

Pancreas.—In postnatal inanition experiments on rats no direct observations have heretofore been made on the weight of the pancreas Therefore no comparisons can be made with postnatal results.

Hatai (1918) gives the weight of the pancreas in the new born rat as 0.0193 gm., or 0.45 per cent body-weight, 4.25 gm. In my normal newborns the weight of the pancreas is 0.0224 gm., or 0.45 per cent body-weight, 4.92 gm.

In my prenatal controls the weight of the pancreas forms 0.35 per cent, 0.38 per cent, 0.35 per cent, 0.45 per cent, and 0.42 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5) Thus, in the smaller prenatal controls (fetuses) the pancreas has a lower relative weight than in the larger rats (fetuses) in which the pancreas has approximately the same relative weight as in the normal newborn rat.

In my test rats the average weight of the pancreas forms 0.31 per cent, 0.37 per cent, 0.42 per cent, 0.37 per cent, and 0.46 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the test rats, as in the prenatal controls, the pancreas in the smaller rats forms a lower percentage of body-weight than in the larger rats, in which the pancreas has a relative percentage weight about the same as that in the normal newborn rat, but the weight of the pancreas is extremely variable in its individual weight and average absolute weight throughout all the groups (Table 5).

In Group 1 the absolute weight of the pancreas in the test rats is less by 10 per cent than in the prenatal controls; in Group 2 it is 2 per cent less; in Group 3 it is 20 per cent heavier; in Group 4, 16 per cent lighter; while in Group 5 it is 9 per cent heavier. The average for all groups shows a deficit of 0.2 per cent in the test rats. From this it is seen that the weight of the pancreas is variable. Its low weight in one group is balanced by its high weight in another. Prenatal inanition probably has very little effect on the relative weight of the pancreas, as its average weight in the test rats is but 0.2 per cent below that in the prenatal norms for the various groups.

Suprarenals.—The weight of the suprarenals, according to the Wistar norm (Donaldson, 1915), is 0.0017 gm. for a rat of 5.1 gm., or 0.034 per cent of the body-weight. Jackson (1913) gives the weight of the suprarenals in the newborn as 0.0019 gm. (0.00188), or 0.039 per cent of the body-weight. In my normal newborns the weight of the suprarenals averages 0.0016 gm. or 0.032 per cent of the body-weight, 4.92 gm.

The weight of the suprarenals in my prenatal controls forms 0.044 per cent, 0.050 per cent, 0.048 per cent, 0.049 per cent, and 0.045 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the suprarenals in the prenatal controls markedly exceeds that of the normal newborn rat.

In my test rats the average weight of the suprarenals forms 0.026 per cent, 0.023 per cent, 0.022 per cent, 0.024 per cent, and 0.024 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the relative weight of the suprarenals in the test rats is less than one-half that in the prenatal controls. On the other hand, however, their relative weight in the prenatal controls greatly exceeds their relative weight at birth. Thus, in the prenatal norm fetuses studied (2.19 gm. to 4.19 gm.), the suprarenals are relatively larger than at birth. They are probably still larger, relatively, in earlier stages, although no data from their earlier size in the rat are available. Jackson (1909) found that in the human fetus the suprarenals increase rapidly to their maximum (relative volume) in the third fetal month, after which they decrease steadily in relative size.

In the test rats the suprarenals show an average weight 52 per cent below that of the prenatal controls (Table 5). The excessively weak growth-tendency of the suprarenals during fetal inanition can not be explained as due to any peculiarity of their normal growth in rats at this time, for, as shown above, the prenatal controls maintain a nearly constant relative (percentage) weight during this period.

In postnatal inanition Stewart (1919) found that in rats kept at birth-weight for 16 days the suprarenals gained 5 per cent in absolute weight over newborn controls, but with longer periods of starvation (underfed from birth to three weeks, body weight 10 gm.), he found that the suprarenals increased markedly in weight (60 per cent and 114 per cent, respectively).

Jackson[19], (1915) also found that the suprarenals manifested a marked growth-tendency in young rats underfed from the age of three weeks to ten weeks, the suprarenals gaining 26 per cent. Stewart (1918), in chronic inanition in young rats, found that the suprarenals gained 48 per cent in absolute weight, while Jackson[19] (1915) found that the suprarenals lost during chronic inanition (26 per cent). In adult rats there is very little or no loss of absolute weight of the suprarenals during either acute or chronic inanition (Jackson,[18] 1915).

From these observations it would appear that the suprarenals in the rat have a weak growth-tendency during inanition in prenatal life and that it is still slight up to sixteen days of age, reaching its maximum at a period between this time and ten weeks, and declining thereafter.

Kidneys.—Jackson (1913) found the kidneys in the newborn rat to weigh 0.46 gm. or 0.97 per cent of the body-weight. The Wistar norm (Donaldson, 1915) for the kidneys in the newborn is 0.48 gm., or 0.97 per cent of the body-weight, 4.95 gm.; in my normal newborns the weight of the kidneys is 0.46 gm. or 0.94 per cent of the body-weight, 4.92 gm.

In my prenatal controls the weight of the kidneys forms 0.58 per cent, 0.63 per cent, 0.54 per cent, 0.71 per cent and 0.70 per cent of the body-weight in Groups 1 to 5 respectively (computed from Table 5). Thus in the prenatal controls the relative weight of the kidneys is less than that in the normal newborn rats. The difference decreases, however, from the small to the larger rats (fetuses). Therefore it is evident that in the rat fetus (from 2 gm. to 4.1 gm.) the kidneys are growing faster than the body as a whole.

In my test rats the average weight of the kidneys forms 0.56 per cent, 0.67 per cent, 0.69 per cent, 0.67 per cent, and 0.71 per cent of the body-weight in Groups 1 to 5 respectively (computed from Table 5). There is very little difference in the relative weight of the kidneys in the test rats and the prenatal controls, but in neither have the kidneys reached the relative (percentage) weight of the body which is normal at birth. In both, the kidneys are growing faster than the body as a whole.

The absolute weight of the kidney is variable. Comparing the test rats and the prenatal controls (Table 5), it is seen that in some groups the absolute weight is higher in the test rats, in others in the prenatal controls. This makes the results seem of questionable significance. This variability can not be attributed to errors in technic, however, as the kidney is an organ easy to remove and clean. In the test rats the absolute weight of the kidneys shows an average weight of 6 per cent above the prenatal controls.

This increase of 6 per cent in the absolute weight of the kidney during prenatal inanition is not nearly so marked as that noted in young rats underfed for various periods after birth. Stewart (Table 6) found that the kidneys showed a gain of 90 per cent in absolute weight in rats kept at a birth-weight for an average of sixteen days; this gain was less marked if the underfeeding was prolonged to three weeks, being 21 per cent (Stewart, 1918). In rats underfed from birth to ten weeks the kidneys showed a gain of 38 per cent. In rats underfed from the age of three weeks to ten weeks, however, Jackson[19] (1915) found that the kidneys increased but 4 per cent; and in chronic inanition in young rats, where the starvation was begun from three weeks to ten weeks after birth and continued to eight months or one year (Jackson,[19] 1915; Stewart, 1918), the kidneys showed a slight loss in weight.

In both acute and chronic inanition in adult rats the kidneys lose in weight relatively slightly less than the body as a whole (Jackson,[18] 1915).

Testes and epididymides.—The Wistar norm (Donaldson, 1915) for the weight of the testes in the newborn rat is 0.004 gm. or 0.081 pre cent of the body-weight, 4.9 gm. Stewart (1919) gives the weight of the testes in the newborn as 0.0027 gm., or 0.053 per cent of the body-weight, 5.08 gm. In my normal newborn the average weight of the testes is 0.0029 gm., or 0.060 per cent of the body-weight, 4.92 gm. There are no prenatal control males in Group 1, consequently no testes for comparison.

In my prenatal controls the weight of the testes forms 0.050 per cent, 0.047 per cent, 0.042, per cent and 0.040 per cent of the body in

Groups 2 to 5, respectively (computed from Table 5). Thus the relative weight of the testes in the prenatal controls is considerably less than that in the newborn rat. It is to be noted that the relative weight is higher in the smaller rats and decreases as the birth-weight is approached. That is, the testes are lagging behind the body-growth as a whole. In order to reach the relative weight normal for the testes at birth, there must necessarily be a period of very active growth in the testes just before birth, in fetuses between the body-weights of 4.1 gm. and 5 gm.

In my test rats the average weight of the testes forms 0.030 per cent, 0.052 per cent, 0.056 per cent, 0.048 per cent, and 0.050 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the testes is slightly higher in the test rats than in the prenatal controls. In both, however, the relative weight of the testes is markedly below that in the normal newborn rat.

The absolute weight of the testes in the test rats averages 16 per cent above the prenatal controls, in four groups.

In postnatal starvation, the testes during the first weeks of life manifest a remarkable growth tendency. Stewart (1919) found that the absolute weight of the testes in rats kept at a constant birth-weight for sixteen days exceeded that of newborn controls by 374 per cent (Table 6), which was the strongest growth tendency exhibited by any organ in the body. In rats underfed from birth to three weeks, the increase in the absolute weight of the testes above that of controls of the same body-weight, 10 gm., is less, being 188 per cent (Stewart, 1918). In a longer period of underfeeding, birth to ten weeks, the testes show a gain in weight of but 51 per cent (Stewart, 1918); while in underfeeding from three weeks of age to ten weeks the testes gain 34 per cent (Jackson,[19] 1915). With prolonged starvation, however, the testes may lose considerably (Stewart, 1918), or may show practically no change (Jackson,[19] 1915).

In both acute and chronic inanition, in adult rats, the testes lose at about the same relative rate as the body as a whole, the loss being slightly more marked in chronic inanition (Jackson,[18] 1915).

From the foregoing it appears that during inanition the testes have their strongest growth tendency just after birth, and that this tendency rapidly decreases with the age of the rat. The weaker growth tendency before birth is evidenced by the weight of the testes during prenatal inanition, which is only 16 per cent above that of the prenatal controls of the same body-weight.

Stewart (1919) gives the weight of the epididymides as 0.0016 gm. in the newborn rat, body-weight 5.08 gm. Hatai (1918) finds that the weight of the epididymides is 0.0025 gm. in the newborn, body-weight of 4.4. gm.; in my normal newborns the weight of the epididymides was 0.0012 gm., body-weight 4.92 gm. This weight is slightly below that given by Stewart and is less than half the value given by Hatai. This difference is probably due to a variation in technic used in cleaning the organ.

There were no male prenatal controls in Group 1 (Table 5).

In the other groups the absolute weight of the epididymides in the test rats is considerably above that of the prenatal controls, with the exception of Group 3, where it is 12 per cent below. The epididymides, however, average 17 per cent higher in the test rats of the various groups. This is about the same as the relation noted in the testes.

In postnatal inanition the epididymides, like the testes, show their strongest growth tendency shortly after birth (Stewart, 1918, 1919); this, however, disappears earlier in the epididymides than in the testes (Table 6).

Ovaries.—Jackson (1913) gives the weight of the ovaries in the newborn rat as 0.00078 gm., body-weight 5.0 gm. Stewart (1919) found their weight to be 0.00110 gm. in the newborn with a body-weight of 4.98 gm. In my normal newborns the weight of the ovaries was 0.00060 gm., body-weight 4.98 gm. This lower weight for the ovaries in my series is probably due to a variation in technic, since it is very difficult to free the ovary from its capsule and from the fallopian tube.

The data on the ovaries are somewhat irregular and conflicting (Table 5). In Groups 1 and 2 the absolute weight of the ovaries in the test rats exceeds that in the prenatal controls by 68 per cent and 6 per cent, respectively; in Group 3 it is 37 per cent below; in Group 4 it is 2.5 per cent above; in Group 5, 33 per cent below. The average weight is 1.3 per cent higher in the test rats. It is hazardous to draw any conclusions from such irregular data, but probably the ovary is very little affected by prenatal inanition.

It is interesting to note, however, that the ovaries in postnatal inanition, in general, show a tendency to increase in weight. This tendency is very slight shortly after birth, since in young rats kept at a constant birth-weight for sixteen days the ovaries showed a gain of but 5 per cent in absolute weight above the controls (Stewart, 1918*a*). In rats underfed from birth to three weeks the ovaries showed a gain of 83 per cent, and in rats starved from birth to ten weeks the gain is 54 per cent, (Stewart, 1918). In rats kept at a constant body-weight from three weeks to ten weeks of age the ovaries lose 27 per cent (Jackson,[19] 1915). In longer periods of inanition Stewart (1918) found a gain of 17 per cent in the weight of the ovaries, while Jackson[19] (1915) found a loss of 54 per cent. It should be remarked, however, that Jackson began the underfeeding at ten weeks instead of at three weeks, as in Stewart's series.

From these data it may be concluded that in prenatal life and up to a few days after birth, the growth tendency in the ovary during inanition is very slight; but that it soon reaches a maximum at a period between two weeks and three weeks of age, declining later.

Thyroid.—The Wistar norm (Donaldson, 1915) foı the weight of the thyroid gland is 0.00145 gm., or 0.027 per cent ofthe body-weight, 5.1 gm. Jackson (1913) gives the weight of the thyroid as 0.0012 gm, body-weight 5.1 gm. In my normal newborn series the thyroid weighed 0.0011 gm, or 0.022 per cent of the body-weight, 4.92 gm.

In my prenatal controls the weight of the thyroid forms 0.040 per cent, 0.030 per cent, 0.032 per cent 0.029 per cent, and 0.029 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the prenatal controls the thyroid forms a relatively higher percentage of the body-weight than in the normal newborn. Since the relative weight of the thyroid decreases as the birth-weight is approached, it is evident that the body as a whole is growing faster than the thyroid.

In my test rats the thyroid forms 0.024 per cent, 0.020 per cent 0.023 per cent, 0.021 per cent and 0.016 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the test rats the thyroid has about the same relative weight as in the normal newborn rat and a lower relative weight than in the prenatal controls.

That the thyroid has been inhibited in its growth in the test rats is evident from a comparison of the absolute weights (Table 5). The absolute weight of the thyroid in the test rats is 33 per cent, 28 per cent, 11 per cent 29 per cent and 45 per cent less than that in the prenatal controls in Groups 1 to 5, respectively. Thus, the absolute weight of the thyroid is lower in all the groups, the average being 29 per cent.

In postnatal inanition the thyroid exhibits a tendency to gain slightly in weight in rats held at maintenance from birth to sixteen days, or starved from birth to three weeks, or from birth to ten weeks (Stewart, 1918, 1919). In longer periods of starvation the thyroid loses quite markedly (Jackson,[19] 1915; Stewart, 1918).

In adult rats, during acute inanition, the thyroid suffers very little or no loss in weight, while during chronic inanition it loses relatively less than the body as a whole (Jackson,[18] 1915).

DISCUSSION

A comparison of the similarities and differences in the growth of the various organs and systems in both prenatal and postnatal inanition is so well shown in Table 6 that a detailed discussion is deemed unnecessary. However, special attention will be called to certain points.

In the systems (Table 6) the "remainder" is constantly above normal in weight in prenatal inanition, while in postnatal inanition it shows a definite loss at various periods throughout the life of the rat.

The visceral group as a whole is subnormal in weight during prenatal inanition. In postnatal inanition, however, it shows a marked tendency to gain in weight in the younger rats (underfed from birth to an average of sixteen days, and from birth to ten weeks, Stewart, 1918, 1919). When the underfeeding is begun at three weeks of age, the visceral group shows a slight gain or just maintains a growth equal to that of the controls. In cases of prolonged underfeeding in the young rats, under one year of age, and in adult life, the visceral group shows a decided loss. It should be noted, as before mentioned, that the gain or loss in the visceral group during inanition is dominated by a loss or gain in weight of certain large organs, such as the liver, lungs, gastro-intestinal tract, and brain. In postnatal inanition the gain in the visceral group compensates for the loss in the "remainder," while in prenatal inanition the converse is true. Thus it is evident that the strongest growth tendency manifested by the visceral group during inanition is at a period just after birth and that it becomes progressively weaker thereafter.

The musculature has a subnormal weight in prenatal inanition and shows but a slight gain (musculature and skeleton combined) in rats underfed from birth to an average of sixteen days of age (Stewart, 1919). It is in rats underfed from birth to three weeks of age that the musculature manifests its greatest gain. This tendency to gain is present, but weaker, in rats underfed for longer periods (Jackson,[19] 1915; Stewart, 1918). In both acute and chronic inanition in adult rats the musculature loses in about the same proportion as the body as a whole (Jackson,[18] 1915). It is evident, therefore, that the growth tendency in the musculature during inanition in the rat is weakest before birth, slightly stronger just after birth, and strongest at a period between birth and three weeks of age, declining thereafter.

The skeleton has a subnormal weight during prenatal inanition and shows a very slight gain in rats starved from birth to an average of sixteen days. In young rats underfed for longer periods, up to adult life, the skeleton shows a marked tendency to gain. During inanition in adult rats the skeleton shows very little change in weight. Thus the growth tendency manifested by the skeleton during inanition is weakest before birth and slightly stronger from birth to sixteen days of age. At three weeks of age, however, it is quite strong, increasing slightly toward adult life. It thus appears that the growth tendency manifested during inanition develops at a relatively later period in the skeleton than in the musculature, but persists longer in the former.

The integument manifests a moderately strong growth tendency during prenatal inanition and just after birth in rats underfed to an average of sixteen days of age. In rats underfed from birth to three weeks of age the integument shows no gain, and in rats starved for longer periods it shows a constant loss in weight.

In postnatal inanition the organs as a general rule manifest their strongest growth tendency in the youngest rats (underfed from birth to an average of sixteen days; Stewart, 1919). The liver, suprarenals and ovaries are exceptions to this rule. The liver loses markedly at this period as compared with a gain at later periods. The suprarenals and ovaries show a very slight gain as compared with marked gain in later periods.

With but few exceptions, those organs which show the most marked gain in the newborn rats (underfed from birth to sixteen days) during postnatal inanition are also above normal in prenatal inanition. The spinal cord is the only exception. Also, all the organs which show a loss or only a slight gain in the newborn rats during postnatal inanition (excepting the indefinite "remainder") are subnormal in weight in prenatal inanition.

It should be noted that the organs and systems that are above the normal weight in prenatal inanition have apparently a lower growth capacity than that shown in postnatal inanition just after birth (Table 6), while those organs and systems which are below normal weight in prenatal inanition (with the exception of the thymus) suffer a greater loss than in postnatal inanition. From the foregoing it is evident in general that the organs and systems of the rat have a weaker growth tendency during prenatal than during postnatal inanition.

The present investigations, therefore, emphasize the fact that in different periods in the life of the rat certain organs and parts react differently, as manifested by their growth during inanition. This is probably due mainly to the varying intensity of the normal growth tendency in the organs and parts at different periods.

Jackson and Stewart (1918) have called attention to the fact that during inanition in the rat the varying intensity of the growth tendency in the different organs and systems depends on four factors: (1) the duration of the period of inanition, (2) the age at which it occurs, (3) its severity, and (4) the character of the inanition.

In prenatal inanition the duration is known (period of starvation of mother). The age is known (length of gestation). The severity is apparently that sufficient to retard the growth of the entire body, an average of 40 per cent as compared with normal newborn controls. Attention may be called to the fact that some of the apparent differences in the growth tendencies of the organs and parts during prenatal and postnatal inanition may be due to the difference in the relative retardation of the body-growth. That is, while the body-growth (average) was retarded 40 per cent in prenatal inanition, it was retarded 66 per cent in Stewart's (1918*a*) series in starvation just after birth. The real nature of the inanition, that is, the amount of reduction in the various nutritive substances reaching the fetus during starvation of the mother, is unknown. The exact character of the inanition to which the fetus is subjected is, therefore, uncertain. However, from the nature of the changes in the relative weight of the organs and parts, it may be stated that the maternal organism during starvation in pregnancy makes extraordinary efforts, as is well known, to keep up the necessary supplies of nutritive substances to the growing fetus and thus protect it from the effects of inanition.

SUMMARY

1. Starvation instituted shortly after copulation in the female albino rat apparently results in an inhibition of pregnancy in the majority of cases. Whether this is due to an inhibition of the implanation, or to death of the ovum, has not been proved.

2. Of fifty-nine female albino rats starved from the eleventh day after copulation, early death of the fetus *in utero* occurred in three cases. Microscopic examination of the swellings in the uterine horns revealed a mass of degenerating tissue, with no evidence of any fetal structures.

3. The length of gestation in the mothers starved during the last half of pregnancy varied from twenty-one days to twenty-six days. Eight of the twenty-two total were above the twenty-three day normal limit, six with a gestation period of twenty-four days, one of twenty-five, and one of twenty six. The average period of gestation was twenty-three days, or one day above the normal average.

4. No abortions or premature deliveries were observed in any of the underfed rats.

5. Of a total of 120 newborn from mothers starved during the last half of pregnancy, forty-one were found dead after delivery. Whether these were dead *in utero*, or died during delivery or afterwards, is uncertain, since at birth they dropped through the wire bottom of the cage. Those living-born that were inclosed within the amniotic sac died of suffocation. Those found living seemed quite vigorous.

6. The average number of observed young per litter, from mothers starved during the last half of pregnancy, was 5.9. The normal average number of young per litter was 7.0 in 1,089 litters (King and Stotsenburg, 1915).

7. A condition of relative sterility apparently results in females starved during the last half of pregnancy. Of the total number starved but four became pregnant a second time.

8. The average weight of the newborn from mothers starved severely during the last half of pregnancy was approximately 3 gm., or 40 per cent below the normal birth-weight of 5 gm.

9. There was no constant relation between the percentage loss in weight of the mother and the weight of the newborn. In general, however, the largest females showed the largest relative loss in weight

and bore the largest young; and the weight of the newborn tends to be inversely proportioned to the severity of the starvation.

10. A prenatal norm for the various systems and organs was established by comparing the relative weights, at the various fetal stages, with those of the normal newborn.

11. During prenatal inanition the tail grows in length faster than the remainder of the body, thus giving rise to relatively long-tailed individuals.

12. Concerning the changes in the general body proportions during prenatal inanition, the head and limbs are slightly above normal weight, counterbalanced by a lower weight in the trunk.

13. The observations on the various systems are summarized as follows: The "remainder" has a weight 25 per cent higher in the test rats than in the prenatal controls. The integument shows a weight averaging 10 per cent above normal in the test rats. The musculature and moist skeleton are slightly subnormal in weight in the test rats, being 5 per cent and 7 per cent, respectively below the prenatal norm. However, the dried skeleton in the test rats has a weight 12 per cent above the prenatal norm. The visceral group, as a whole, has a markedly subnormal weight in the test rats, being 18 per cent below the prenatal norm. This is due chiefly to the subnormal weight of the liver and lungs. The low weight in the visceral group evidently compensates for the high weight of the "remainder."

14. The weight changes observed in the individual organs in the test rates during prenatal inanition, as compared with normal fetuses of the same body-weight, show the following average percentage differences in weight:

	Per cent		Per cent
Brain	+12	Intestines with contents	+15
Spinal cord	− 0.26	Intestines empty	− 2
Eyeballs	+31	Pancreas	− 0.26
Thymus	−21	Suprarenals	−52
Heart	+ 8	Kidneys	+ 6
Lungs	−39	Testes	+16
Liver	−45	Epididymides	+17
Spleen	+34	Ovaries	+ 1.3
Stomach with contents	− 4	Thyroid	−29
Stomach empty	+ 6		

15. In general, therefore, it may be stated that the spleen, eyeballs, epididymides, testes, and brain manifest a fairly strong growth

tendency during prenatal inanition, the tendency decreasing in the order named. A slight growth tendency is manifested by the heart, kidneys, stomach, and ovaries, decreasing in the order named. A retardation in growth during prenatal inanition increasing in the order named is shown by the pancreas, spinal cord, intestines, thymus, thyroid, lungs, liver, and suprarenals.

16. In general, the organs and systems that have been found to gain greatly during postnatal inanition (in the newborn rats) are, during prenatal inanition, also above normal weight, but to a much less degree; while those below or but slightly above normal weight during postnatal inanition show a still greater loss in prenatal inanition. Thus, during inanition, the growth impulse of the organs appears as a rule weaker in the prenatal than in the postnatal period. It should be noted, however, that the exact nature of the prenatal inanition is somewhat uncertain.

BIBLIOGRAPHY

1. von Bechterew, W.: Über den Einfluss des Hungers auf die neugeborenen Thiere insbesondere auf das Gewicht und die Entwickelung des Gehirns. Neurol. Centralbl 1895, xiv, 810–817.

2. Conrow, S. B.: Cited by Donaldson, 1915.

3. Daniel, J. F.: Observations on the period of gestation in white mice. Jour. Exper. Zool., vol. 9, 1910, ix, 865–870.

4. Donaldson, H. H.: The effect of underfeeding on the percentage of water, on the ether-alcohol extract, and on the medullation in the central nervous system of the albino rat. Jour. Comp. Neur., 1911, xxi, 139–145.

5. Donaldson, H. H.: The rat, reference tables and data for the albino rat (*Mus norvegicus albinus*) and the Norway rat (*Mus norvegicus*). Memoirs of the Wistar Institute of Anatomy and Biology, Philadelphia, 1915. (No. 6) 278 pp.

6. Evvard, J. M.: Nutrition as a factor in fetal development. Proceedings American Breeders' Association, 1912, viii, 549–560.

7. Evvard, J. M., Dox, A. W., and Guernsey, S. C.: The effect of calcium and protein fed pregnant swine upon the size, vigor, bone, coat, and condition of the offspring. Am. Jour. Physiol., 1914, xxxiv, 312–325.

8. Hart, E. B., McCollum, E. V., Steenbock, H. and Humphrey, G. C.: Balanced rations from restricted sources. Their physiological effect on growth and reproduction. Scient. Am. Supp., 1919, No. 2256, 202–203; See Research Bulletin No. 17, Univ. of Wisc. Agr. Experiment Station, June, 1911.

9. Hatai, S.: The effect of partial starvation on the brain of the white rat. Am. Jour. Physiol., 1904–1905, xii, 116–127.

10. Hatai, S.: Preliminary note on the size and condition of the central nervous system in albino rats experimentally stunted. Jour. Comp. Neur., 1908, xviii, 151–155.

11. Hatai, S.: On the weights of the abdominal and the thoracic viscera, the sex glands, ductless glands, and the eyeballs of the albino rat (*Mus norvegicus albinus*) according to body-weight. Am. Jour. Anat., 1913–1914, xv, 87–119.

12. Hatai, S.: On the weight of the thymus gland of the albino rat (*Mus norvegicus albinus*) according to age. Am. Jour. Anat., 1914, xvi, 251–257.

13. Hatai, S.: The growth of the body and organs in albino rats fed with a lipoid-free ration. Anat. Rec., 1915, ix, 1–20.

14. Hatai, S.: On the weight of the epididymis, pancreas, stomach and of the submaxillary glands of the albino rat (*Mus norvegicus albinus*) according to body-weight. Am. Jour. Anat., 1918, xxiv, 71–89.

15. Huber, G. C.: The development of the albino rat (*Mus norvegicus albinus*). I. From the pronuclear stage to the stage of mesoderm anlage; end of the first to the end of the ninth day. Jour. Morph., 1915, xxvi, 247–358.

16. Jackson, C. M.: On the prenatal growth of the human body and the relative growth of the various organs and parts. Am. Jour. Anat., 1909, ix, 119–165.

17. Jackson, C. M.: Postnatal growth and variability of the body and of the various organs in the albino rat. Am. Jour. Anat., 1913-1914, xv,1–68.

18. Jackson, C. M.: Effects of acute and chronic inanition upon the relative weights of the various organs and systems of adult albino rats. Am. Jour. Anat., 1915, xviii, 75–116.

19. Jackson, C. M.: Changes in the relative weights of the various parts, systems, and organs of young albino rats held at a constant body-weight by underfeeding for various periods. Jour. Exper. Zool., 1915, xix, 99–156.

20. Jackson, C. M., and Lowrey, L. G.: On the relative growth of the component parts (head, trunk and extremities) and systems (skin, skeleton, musculature and viscera) of the albino rat. Anat. Rec., 1912, vi, 449–474.

21. Jackson, C. M. and Stewart, C. A.: The effects of underfeeding and refeeding upon the growth of the various systems and organs of the body. Minn. Med., 1918, i, 403–414.

22. Jackson, C. M. and Stewart, C. A.: The effects of inanition in the young upon the ultimate size of the body and of the various organs in the albino rat. Jour. Exp. Zool., 1920, xxx, 97–128.

23. Jonson, A.: Studien über die Thymusinvolution. Die akzidentelle Involution bei Hunger. Arch. f. mikr. Anat., 1909, lxxiii, 390–443.

24. King, Helen D.: Some anomalies in the gestation of the albino rat (*Mus norvegicus albinus*). Biol. Bull., 1912–1913, xxiv, 377–391.

25. King, Helen D.: On the weight of the albino rat at birth and the factors that influence it. Anat. Rec., 1915, ix, 213–231.

26. King, Helen D.: On the postnatal growth of the body and of the central nervous system in albino rats that are undersized at birth. Anat. Rec., 1916–1917, xi, 41–52.

27. King, Helen D., and Stotsenburg, J. M.: On the normal sex ratio and the size of the litter in the albino rat (*Mus norvegicus albinus*). Anat. Rec., 1915, ix, 403–420.

28. Kirkham, W. B., and Burr, H. S.: The breeding habits, maturation of eggs and ovulation of the albino rat. Am. Jour. Anat., 1913–1914, xv, 291–317.

29. Lataste F.: Des variations de durée de la gestation chez les mammiferes et des circonstances qui déterminent ces variations; théorie de la gestation retardée. Comp. Rend Soc. de biol., 1891, G. S., iii, pt. 2, 21–31.

30. Lowrey, L. G.: Prenatal growth of the pig. Am. Jour. Anat., 1911–1912, xii, 107–138.

31. Lowrey, L. G.: The growth of the dry substance in the albino rat. Anat. Rec., 1913, vii, 143–168.

32. Mühlmann, M.: Russische Literatur über die Pathologie des Hungerns (der Inanition). Zusammenfassendes Referat. Centrabl. f. allg. Pathol., 1899, x, 160–220; 240–242.

33. Osborne, B., and Mendel, L. B.: Nutritive properties of proteins of the maize kernel. Jour. Biol. Chem., 1914, xviii, 1–16.

34, Paton, D. N.: The influence of diet in pregnancy on the weight of the offspring Lancet, 1903, ii, 21–22.

35, Prochownick, L.: Ein Versuch zum Ersatze der künstlichen Frühgeburt. Centrabl. f. Gynäk., 1889, xiii, 577–581.

36. Prochownick., Uber Ernährungscuren in der Schwangerschaft. Therap. Monats., 1901, xv, 387–403; 446–463.

37. Reeb, M.: Uber den Einfluss der Ernährung der Muttertiere auf die Entwicklung ihrer Früchte. Beitr. z. Geburtsh. u. Gynäk., 905, ix, 395–411.

38. Rudolski, L. V.: On pregnancy in animals in cases of insufficient nourishment of the organism; experimental investigation performed upon rabbits and a dog. Dissert. St. Petersburg, 1893, Muller and Bogelman, 114 pp., 1899.

39. Stewart, C. A.: Changes in the relative weights of the various parts, systems, and organs of young albino rats underfed for various periods. Jour. Exper. Zool., 1918, xxv, 301–353.

40. Stewart, C. A.: Changes in the weights of the various parts, systems and organs in albino rats kept at birth weight by underfeeding for various periods. Am. Jour. Physiol., 1919, xlviii, 67–78.

41. Stotsenburg, J. M.: Cited by Donaldson, 1915.

42. Stotsenburg, J. M.: The growth of the ferus of the albino rat from the thirteenth to the twenty-second day of gestation. Anat. Rec., 1915, ix, 667–682.

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THE GROWTH OF THE CENTRAL NERVOUS SYSTEM IN THE HUMAN FETUS AS EXPRESSED BY GRAPHIC ANALYSIS AND EMPIRICAL FORMULAE

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THIRTY-EIGHT FIGURES

CONTENTS

Introduction.. 405
Material and methods.. 407
    Material.. 407
    Methods of collecting data...................................... 409
    Methods of treating data.. 413
Summary of observations... 417
    Growth of the central nervous system as a whole................. 417
    Growth of the encephalon.. 419
    Growth of the cerebrum.. 423
    Growth of the cerebellum.. 435
    Growth of the pons and medulla.................................. 442
    Growth of the midbrain.. 447
    Growth of the spinal cord....................................... 451
Discussion.. 456
    Growth of the central nervous system as a whole................. 458
Summary... 488

INTRODUCTION

The growth of the human central nervous system has long been a matter of interest and many studies on this subject have been published, some of the earlier ones dating back almost a century. These investigations have given us a general knowledge of the growth of the brain as a whole from birth to maturity and have furnished us some information regarding the modifications in absolute and relative size of the various brain parts in early postnatal life.

Our knowledge of the growth of the central nervous system in the prenatal period is much less complete. While the numerous studies on the morphogenesis of the brain and spinal cord in the first trimester of fetal life enable us to draw some general conclusions concerning the early prenatal growth of these structures, there are practically no quantitative data available for this period. Data on the later prenatal growth of the brain are more extensive, and a survey of the literature gives about 500 published records of the weight of the brain between the third fetal month and birth. The more important of these collections are those of Rudinger ('77), Brandt ('86), Arnovljevič ('84), Michaelis ('06), Jackson ('09), and Valtorta ('09). A small amount of this material has been presented in graphic form by Zangemeister ('11). The only collection of records of the weights or volumes of the various parts of the brain in fetal life seems to be a short series of figures on the cerebrum, cerebellum, and brain stem published by Valtorta ('09).

The spinal cord has received far less attention than the brain, doubtless because of its smaller size and the technical difficulties of its removal. Our knowledge of the growth of the cord in postnatal life is very incomplete, being limited to the data of Pfeister ('03) and Danielbekoff ('85). Information regarding the changes in fetal life is apparently confined to a study by Giese ('98), published as a St. Petersburg dissertation, which is available only in abstract at the present time.

The following study was undertaken with the hope that a part of this large gap in our knowledge of human growth might be spanned by the systematic examination and measurement of the brain and spinal cord in a large series of human fetuses ranging from the second fetal month to birth, and by the treatment of these data by some of the more modern methods of statistical and graphic analysis. The work was done under the direction of Dr. R. E. Scammon, to whom the writer is very much indebted for constant advice and aid throughout the entire study.

MATERIAL AND METHODS

Material

The material used in this study consisted of 156 human fetuses. Fifty-four of these specimens were males, fifty-six were females, and the sex of forty-six was unknown. The specimens ranged from 3.1 to 53.6 cm. in total or crown-heel length and were quite evenly distributed between these extremes. At least one specimen was available for each centimeter interval of crown-heel length and in many of the centimeter intervals below 30 cm. there were three, four, or five specimens. All of the material was selected from a much more extensive series of cases, with a view to securing specimens in which the brains were well preserved; however, a number of brains which were rather soft were used for certain measurements which were not affected by this condition.

The great majority of the specimens were fixed in 10 per cent formalin to which 1 per cent chromic acid had been added in some instances, and all were afterwards preserved in 10 per cent formalin. Five specimens of the entire series were fixed in Zenker's or Müller's fluid and were subsequently preserved in 70 per cent alcohol. All of the material had been in the preservation for six months or more.

The effect of formalin fixation upon the fetal brain must be known in order to interpret the data correctly. It is unfortunate that no comparison has been made between fresh and preserved material. The fresh brain of the fetus is too friable for any delicate, quantitative measurements to be taken upon it. Consequently, fixation was prerequisite to the collection of the material for this study.

The only checks upon the relationship of fixed and unfixed material at our disposal consist of, 1) the determination of the effects of formalin upon the size of the fetal body and, 2) the relation of the curves of fresh brain weight to that of fixed brain volume.

Several investigators have determined the effects of formalin fixation on the fetus. Patten and Philpott ('21) record an average increase in the crown-rump length of 4.8 per cent in a series of twenty-two pig embryos which had been in 10 per cent formalin for six months. Schultze ('19) reports an average gain in crown-rump length of 2.3 per cent in a group of eighteen human fetuses which had been in 10 per cent formalin for nine months. The average gain in head length and head breadth of the same series was 1.1 per cent and 5.2 per cent, respectively. Calkins ('21) has found that the effect of fixation on the several diameters of the head is very small and that formalin injection causes the greatest part of this by a distention of the superficial tissues of the scalp. The fetal cranium increases, therefore, very little in size when it is fixed by formalin. The brain, on the other hand, is supposed to gain greatly in volume. King ('10) obtained a percentage gain in weight of from 30 to 50 when the brains of several white rats were subjected to formalin fixation. Such an increase in brain weight or volume could take place in the fetus only at the expense of the dural and subdural spaces, since the circumference and the diameters of the fetal head are but little affected. However, these spaces were found to be quite large in most of the preserved specimens in this series. The volume of the brain, therefore, could not have been increased to any great extent.

The relationship of the curve of fresh brain weight to that of fixed brain volume can be compared readily by tables 2 and 3. Table 2 shows the calculated volume of the central nervous system for each 5 cm. C H interval. Table 3 sets forth the empirically determined values for weights of fresh fetal brains collected from the literature. In each respective C H interval the weight is seen to be slightly greater than is the volume. This difference may be caused in part by the formalin fixation, but the greater part seems to be due to the fact that midsagittal sections of the brain were made before volumes were determined and that intraventricular fluid was lost by this procedure. On the whole, therefore, it is doubtful if there is any considerable change of the fetal brain volume upon formalin fixation.

Five cases of the series were subjected to Zenker- or Müller-alcohol fixation instead of formalin. The effects of various fixing fluids upon brain tissues have been determined by King ('10) and Hrdlička ('06). The work of King was done upon the brain of the rat, and is analogous, in all probability, to the effects of the fixing fluids upon the fetal brain. Calculated from her findings, the absolute values of the five fetal brains subject to Zenker- or Müller-alcohol fixation would be 10 to 40 per cent lower than the brains which were fixed by formalin. Three of the fetal brains in the present series which were fixed by the Zenker- or Müller-alcohol method lie in the C H interval of 5 to 10 cm. and two are in the C H interval of 10 to 15 cm. A glance at figure 2 shows that these cases adhere closely to the central tendency. Hrdlička subjected the brains of twenty-seven mammals and birds to 10 per cent formalin fixation. Ten sheep brains showed an average increase of 13 per cent after one month of fixation; seven brains of birds an average gain of 20 per cent and six brains of various mammals about 24 per cent. He left the brains in 10 per cent formalin for eighteen months, and then found that they had decreased in size to about 92 per cent of their original weight.

From the results of these investigators as well as the data of this series, it is obvious that 10 per cent formalin fixation has a comparatively slight effect upon the volumetric determination of the fetal brain.

Methods of collecting data

The magnitudes and proportions of the various parts of the central nervous system were determined by several different methods—by lineal measurements, by weighing and determining the volume of each part, by making tracings of median sagittal sections, and by photographing the lateral surfaces of the specimens. The details of these methods and the descriptions of the measurements taken will be considered separately.

Lineal measurements. All lineal measurements were made with a steel vernier caliper which could be read accurately to 1 mm. by the major and to 0.1 mm. by the minor scale. They were made with the brain and spinal cord in situ and always represented the shortest distance between two given points.

Weight. The ponderal determinations were made on a scale accurate to 0.01 gram. Before weighing in every instance the brain part was stripped of its meningeal coverings and was placed on a pad of dry gauze for 30 seconds to remove approximately the same amount of surplus fluid in each case. Weights were always taken upon preserved material.

Volumes. The volumetric determinations were made with a special apparatus constructed according to a plan suggested by Prof. L. W. Jones, formerly of the Department of Chemistry of the University of Minnesota. A sketch of this device is shown in figure 1. It consists of an iron chemical stand (*A*) to which a clamp (*B*) is attached. This clamp holds a hard-rubber stopper (*C*), to which is attached a slender wire (*D*) about 15 cm. in length. A small disk of mica about 1 cm. in diameter slides freely on this wire. The wire is suspended in a jar or wide-mouthed bottle (*F*) which has a spigot at its base and which is partially filled with water. In using the apparatus the water in the bottle is drawn off until the mica disk which floats on its surface touches the hair line on the wire. The mass to be measured is then placed in the bottle and the level of the fluid rises, carrying the disk with it. The water is then drawn off into a beaker of known weight until the mica disk has sunk again to the level of the hair line on the wire. The beaker with the contained water is then weighed and the known weight of the beaker is subtracted from the total, thus giving the weight of the water displaced by the brain part. After the proper temperature correction, this value can be converted into a measure of volume. With practice and proper precautions, it is possible to determine small volumes quite accurately with this apparatus. When working with small bodies, it is desirable to use a bottle with a capacity of not over 30 to 40 cc. A difference of approximately 0.1 cc. in volume can be determined without trouble if a small container is used.

The lineal, volumetric, and ponderal determinations made were as follows:

1. C H: Crown-heel length, or total body length; from the vertex to the tip of the heel.
2. C R: Crown-rump length, or the sitting height; from the vertex to the tip of the coccyx.

3. F O: Fronto-occipital diameter; from the frontal pole to the occipital pole of the cerebral hemisphere. The frontal pole is defined as that point where the anterior, lateral, and inferior surfaces of the frontal lobes meet. In large brains, in situ, this point is adjacent to the crista galli. The occipital pole is defined as that point where the posterior, lateral, and the interior surfaces of the occipital lobes meet.

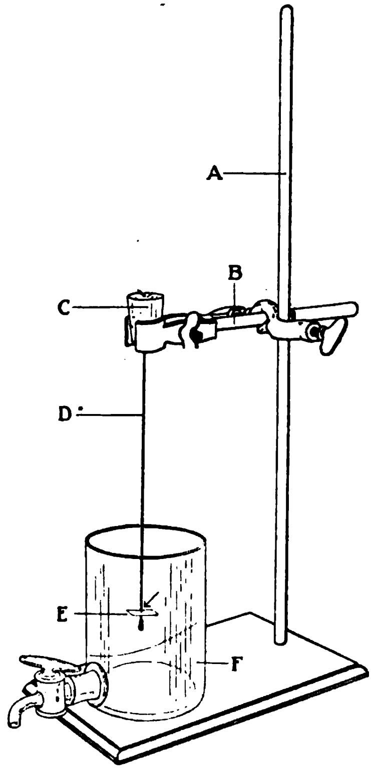

Fig. 1 A figure representing the volumetric apparatus used in the collection of data. *A*, iron standard; *B*, clamp; *C*, stopper; *D*, wire; *E*, movable isinglass disk; *F*, bottle with spigot. The arrow indicates a hair line upon the wire.

4. T T: Temporal diameter; from the right temporal pole to the left temporal pole of the cerebral hemispheres. The temporal pole is defined as the most lateral point on the anterior

projection of the temporal lobe. This point becomes less definite in large fetuses, but can still be recognized with sufficient accuracy.

5. F S: Frontospinal length; from the frontal pole of the cerebral hemisphere to the point of origin of the first cervical nerve. This measurement was taken to the middle of the body of the first cervical vertebra, for it was sometimes difficult to identify the first cervical nerve because of error in securing exact midsagittal sections of the brain and the spinal cord.

6. S C: Spinal cord length; from the point of origin of the first cervical nerve to the tip of the conus medullaris; the measurement was made with cord in situ.

7. B C: Brain and cord length; the sum of S C (6) and F S (5).

8. P L: Pons length; the greatest inferior length of the pons.

9. C L: Colliculi length; from the most anterior point of the superior colliculus to the most posterior point of the inferior colliculus.

10. V L: Vermis length; the greatest length of the vermis cerebelli parallel with the axis of the pons and medulla.

11. V H: Vermis height; the greatest height of the vermis cerebelli perpendicular to the long axis of the pons and medulla.

12. V S C: Volume of the spinal cord; cord taken from the first cervical nerve to the tip of the conus medullaris and freed of meninges and nerve roots.

13. V P M: Volume of the pons and medulla; pons and medulla cut posteriorly at the first cervical nerve and anteriorly just in front of the pons, meninges removed.

14. V M B: Volume of the midbrain; the midbrain was cut just in front of the pons posteriorly and just in front of the superior colliculi and through the pedunculi cerebri behind the mammillary bodies anteriorly, meninges removed.

15. V C: Volume of the cerebellum; the velum medullaris was severed anteriorly and posteriorly to free the cerebellum from the pons and medulla, meninges removed.

16. V R H: Volume of the right hemisphere, meninges removed.

17. V L H: Volume of the left hemisphere, meninges removed.

18. V B H: Volume of both hemispheres: computed by adding V R H (16) and V L H (17).

19. V E B: Volume of the entire brain or encephalon computed by adding 13, 14, 15, 16, and 17. This method was found to be more accurate in dealing with the soft brains than to take the actual volumes of all the parts, because of the possible loss of brain tissue in handling.

20. V C N S: Volume of the central nervous system; found by adding the volume of the spinal cord (12) to the entire brain or encephalon volume (19).

The ponderal determinations corresponding to the volumetric measurements were taken and are included in table 41.

Methods of treating data

While the accuracy of data of the kind here presented depends upon the nature of measures employed and the care with which these measures are determined, their significance can only be ascertained by the use of a variety of methods of graphic and numerical analysis. A number of these methods have been used in the present study. They may be arranged in order of procedure in five main groups, namely: 1) Construction of field graphs with points of central tendency and establishment of preliminary curves by inspection. 2) Reduction of these preliminary curves, as established by inspection, to empirical fomulae based on total body length, and construction of primary data tables. 3) Calculation of values at 5-cm. intervals of body length, calculation of absolute and percentage increments for each 5-cm. interval of body length, calculation of newborn ratios for each 5-cm. interval of body length, and expression of these values in the graphic form. 4) Conversion of the various values as determined by empirical formulae from functions of the body length to functions of the age in fetal months by interpolation on the basis of Mall's ('12) tables of crown-heel length in fetal life. Determination of the monthly percentage and absolute increment on the basis of these conversions; graphic expression of these values. 5) Determinations of the relative weights of the various parts of the central nervous system as compared to that of the encephalon. These several methods of analysis will now be considered in more detail.

1. *Construction of field graphs and establishment of preliminary curves by inspection.* The data secured for each measurement of the central nervous system were first plotted on a field graph in which the length of the body (C H) was used for the abscissa and the measurement in question for the ordinate. The material was then divided into classes on the basis of 5-cm. intervals of crown-heel length and the arithmetic mean or average and the median were determined for each of these classes. These means were then indicated in the graphs by special symbols, their exact position being determined by weighting for the distribution of the cases according to crown-heel length in the 5-cm. intervals. A preliminary curve was then drawn by inspection on the basis of the combined evidence furnished by the position of the arithmetic mean, the median, and the general distribution of the cases. This method has distinct advantages over the practice of establishing curves of inspection on the basis of the arithmetic mean alone, particularly in those instances where a curve is rising rapidly in a single interval or where the cases are not regularly distributed. The use of both the arithmetic mean and the median enables one to correct for chance deviations in the mean alone with considerable confidence, particularly when the cases are all spread before one on the field graph.

2. *Reduction of preliminary curves of inspection to numerical expression by means of empirical formulae.* The curve of each value as determined by inspection was reduced to numerical expression in the form of an empirical formula on the crown-heel or total length of the body expressed in cm. This procedure in no way increases the reliability of the curve as determined by inspection nor does it increase the accuracy of the points upon which it is based, but it has several important advantages, for it permits an accurate and abbreviated expression of the curve, facilitates exact interpolation and the conversion of values into different scales and forms of expression, and, in some cases, aids in classifying the curves as to form.

The empirical formulae expressing the curves obtained from the material are of several types. As certain of the lineal dimensions of the brain are straight lines when plotted against crown-heel length, they may be expressed by the formula:

$$Y = aX + b$$

where Y is the value in question expressed in cm., X is the crown-heel length in cm., and a and b are empirically determined constants.

The growth of other lineal dimensions of the central nervous system is not so simply related to the lineal growth of the body as a whole and the expression of this relation is more complex. But all may be represented by formulae having the general form:

$$Y = (aX)^b \pm c$$

where Y is the value in question (in cm.), X is the crown-heel length of the body (in cm.), and a, b, and c are empirically determined constants, b being a fractional exponent. Curves corresponding to formulae of this type may also be expressed fairly satisfactorily in the logarithmic form:

$$Y = aX + b \log X \pm c$$

which will be recognized as the formula which Hatai employed with great success in the study of the growth of the various organs of the albino rat and which is regarded by him as of fundamental importance as exemplifying the application of the law of Maupertuis to the process of growth. However, the exponential form has been found the more convenient for application in the present work.

The formulae for the expression of the inspected curves of volumes of the various parts of the central nervous system have as their simplest form:

$$Y = (aX)^b$$

which is modified in certain instances to:

$$Y = (aX)^b \pm c$$

and in others to:

$$Y = d\,[(aX)^b \pm c]$$

In these formulae Y is the value in question in cc., X is the crown-heel length in cm., and a, b, c, and d are constants, b being always an exponent with a value greater than 1.

Having obtained calculated values for the different measurements under consideration, tables of each dimension were drawn up in some detail. These are tables 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 36, 38 of the present publication. In each of these is given the crown-heel length in 5-cm. intervals, the average crown-heel length, the maximum, minimum, and arithmetic mean (average) of the considered measurement in the interval, the calculated mean for the same measurement, and the absolute difference between the calculated and the observed means. Both the calculated and observed means are recorded to the nearest millimeter for length and to the nearest 0.1 cc. for volumes in these tables.

3. *Calculation of secondary tables.* Secondary determinations made on the basis of the above calculations are included in tables 2, 4, 5, 6, 10, 12, 14, 16. These include the absolute value of each measurement, as determined by calculation with the empirical formula, for each 5 cm. of body length from 5 to 55 cm., and the percentage and the absolute increment of these values for each 5-cm. interval between these points.[1] Included in these tables is also the ratio of the calculated value of the measurement at each 5 cm. of the total body length to the calculated value of the new-born. It was assumed that the value at 50 cm. of crown-heel length represented the new-born and the calculated values for the 5-cm. points below 50 are expressed in per cents of this one. The reduction of values to this common scale is of great convenience, since it permits their direct comparison regardless of their absolute magnitudes.

4. *Conversion of the various values from functions of the crown-heel length to functions of the age in fetal (lunar) months.* This was done by calculating the values by means of the empirical formulae

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[1] The percentage increment was determined in the customary manner. The absolute value at the beginning of an interval is subtracted from the absolute value at the close of the same interval. The result is divided by the absolute value at the beginning of the interval and the quotient thus obtained is multiplied by 100 in order to reduce it to a percentage basis. The percentage increment is the only simple form of expression of relative growth now in use which is at all satisfactory. However, it gives only a rough approximation of the actual rate of growth in a given interval.

from Mall's tables of the relation of crown-heel length to age in prenatal life (Keibel and Mall, Human Embryology, vol. 1, p. 199). The results obtained by this procedure are not to be regarded as final, for the exact relation between body length and age in fetal life is still open to question. They are included, however, because they give, in a rough way at least, some concept of the relation of the growth of the central nervous system to time in the prenatal period and because they aid in the interpretation of its percentage increment. Since Mall's table stops at 270 days, it has been extended by graphic exterpolation to ten full lunar months (280 days) and the length at this age (51.5 cm.) was considered as the norm for the new-born in this type of calculation. The monthly percentage increments of the principal volumetric determinations were calculated secondarily from the values obtained in this manner. They are shown in table 42.

5. *Determination of the relative weights of the various parts of the central nervous system in terms of per cents of the encephalon* is an obvious procedure which needs no particular description. The results obtained are shown in table 40.

SUMMARY OF OBSERVATIONS

Growth of the central nervous system as a whole

The curve of the absolute volume of the central nervous system (fig. 2), when based upon crown-heel or total body length, is concave like all other curves of volume growth of the fetal organs. It may be expressed by the empirical formula:

$$\text{Central nervous system volume (cc.)} = [0.114\ (\text{C H length cm.})]^{3.34} + 2.0$$

The absolute volume of the central nervous system is about 7 cc. at 10 to 15 cm. (C H). This increases steadily to 36 cc. at 25 cm. (C H), and is then deflected upward sharply to reach 337 cc. at 50 cm. (C H).

When calculated according to age in fetal months, the absolute volume of the central nervous system (fig. 34, curve I) is found to be 2 cc. at the beginning of the third month, rising to 36 cc. at the beginning of the sixth month, and to about 340 cc. at birth.

The rate of growth of the volume of the central nervous system as determined by the 5-cm. interval percentage increment (page 413), (fig. 26, curve I) is approximately 120 per cent for the 10-to-15-cm. interval and descends gradually to about 40 per cent for the 50-to-55-cm. interval.

TABLE 1

Volume of the central nervous system

Formula: Volume of the central nervous system (cc.) $=$ $[0.114\ (\text{crown-heel length cm.})]^{3.34} + 2.0$

(146 cases)

CROWN-HEEL LENGTH		OBSERVED VOLUME OF CENTRAL NERVOUS SYSTEM			CALCULATED VOLUME OF CENTRAL NERVOUS SYSTEM	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5	3.9	0.7	0.1	0.3			4
5 to 10	7.2	2.4	0.6	1.3			12
10 to 15	12.2	8.6	2.1	5.4	5.0	−0.4	21
15 to 20	16.8	22.5	3.0	12.5	10.8	−1.7	16
20 to 25	22.6	49.5	17.4	31.1	25.6	−5.5	19
25 to 30	27.1	65.4	24.7	46.9	45.3	−1.6	12
30 to 35	32.8	144.2	45.8	81.8	83.9	+2.1	18
35 to 40	37.2	222.8	102.2	141.4	126.7	−14.7	17
40 to 45	42.2	256.9	145.3	197.7	187.6	−10.1	12
45 to 50	48.0	412.5	207.0	306.0	294.0	−12.0	7
50 to 55	52.2	414.3	332.3	367.5	388.5	+21.0	8

TABLE 2

Calculated volume of the central nervous system at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	VOLUME OF CENTRAL NERVOUS SYSTEM	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cc.*	*cc.*	*per cent*	*per cent*
5				
10	3.6			1.1
15	8.0	4.4	122.0	2.4
20	17.7	9.7	121.2	5.3
25	35.0	17.3	97.6	10.4
30	62.8	27.8	79.4	18.6
35	103.5	40.7	65.0	30.7
40	160.9	57.4	55.4	47.7
45	237.3	76.4	47.5	70.3
50	336.8	99.5	41.9	100.0
55	462.2	125.4	37.2	137.0

The percentage increment, when calculated for time, is about 600 in the fourth fetal month. This drops to 185 in the fifth month and to 22 per cent in the tenth month.

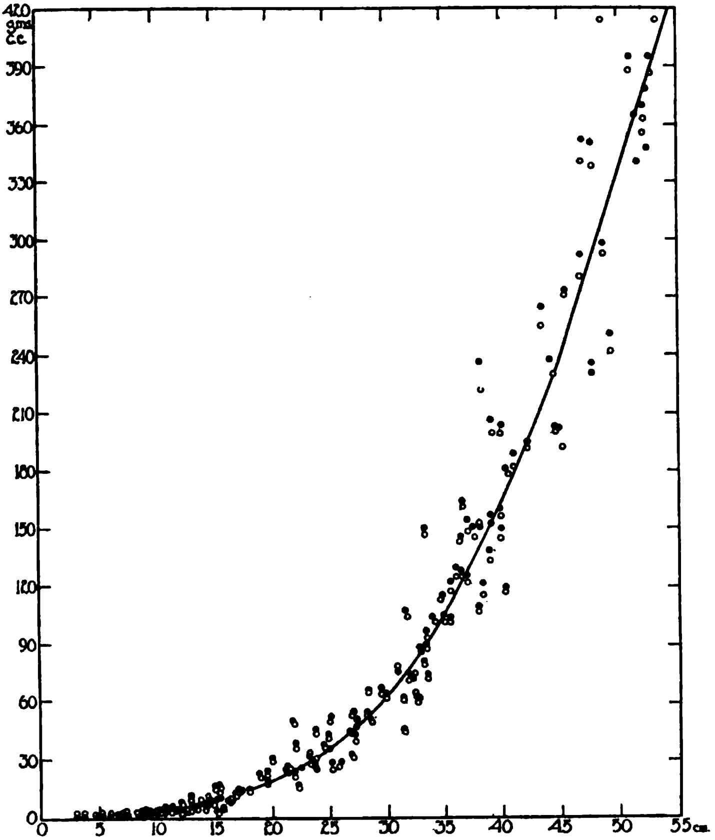

Fig. 2 Field graph and curve of the growth of the central nervous system in fetal life. Abscissa: total body length in cm. Ordinate: central nervous system weight and volume in grams (cc.). Individual cases are indicated by solid dots (for weight) and by circles (for volume). Curve drawn to the formula: $Y = (0.114X)^{3.34} + 2.0$. (Data from tables 1 and 2.)

Growth of the encephalon

The curve of the absolute volume of the entire brain (fig. 3) when based on crown-heel length is a concave curve expressed by the empirical formula:

Encephalon volume (cc.) = (0.125 (C H length cm.))$^{3.16}$ + 1.5

The absolute volume of the entire brain when based on crown-heel length (fig. 3) is about 3.5 cc. at 10 cm. (C H). This increases to 38 cc. at 25 cm. (C H) and then more rapidly to 330 cc. at 50 cm. (C H).

TABLE 3

Encephalon volume

Formula: Encephalon volume (cc.) = $(0.125 \text{ crown-heel length cm.})^{3.16} + 1.5$
(144 cases)

CROWN-HEEL LENGTH		OBSERVED VOLUME OF ENCEPHALON			CALCULATED VOLUME OF ENCEPHALON	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5	3.9	0.7	0.1	0.3			4
5 to 10	7.2	1.8	0.6	1.2	2.2	+1.0	11
10 to 15	12.3	9.5	2.0	5.4	5.4	0	21
15 to 20	16.9	22.4	2.8	11.9	12.1	+0.2	16
20 to 25	22.3	48.8	16.7	30.8	27.1	−3.7	19
25 to 30	27.1	64.7	27.3	45.8	48.7	+2.9	12
30 to 35	32.2	106.3	45.2	76.5	83.0	+6.5	17
35 to 40	37.2	221.8	101.2	132.1	130.1	−2.0	18
40 to 45	42.8	255.1	144.1	191.2	201.5	+10.3	10
45 to 50	48.0	409.4	226.7	299.1	289.0	−10.1	8
50 to 55	52.2	412.3	331.4	364.9	376.5	+11.6	8

TABLE 4

Calculated volume of encephalon at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	VOLUME OF THE ENCEPHALON	INCREMENT IN EACH 5-CM. INTERVAL OF CROWN-HEEL LENGTH		RATIO TO NEW-BORN
cm.	*cc.*	*cm.*	*per cent*	*per cent*
5				
10	3.5			1.1
15	8.4	4.9	140.0	2.5
20	19.6	11.2	133.5	6.0
25	38.1	18.5	94.4	11.6
30	66.6	28.5	74.8	20.2
35	107.6	41.0	61.5	32.7
40	163.3	55.7	51.8	49.6
45	236.1	72.8	44.5	71.8
50	328.9	92.8	39.4	100.0
55	444.0	115.1	35.0	135.0

When calculated to age in fetal months (fig. 34, curve I), the volume of the entire brain is about 1 cc. at the beginning of the third month. It increases to 14 cc. by the first of the fifth month, and reaches the value of 330 cc. by birth.

The rate of growth of the encephalon when determined by 5-cm. percentage increment (fig. 26, curve II) is approximately

TABLE 5

Calculated weight of the encephalon (based on collected data) at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	WEIGHT OF THE ENCEPHALON	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*grams*	*grams*	*per cent*	*per cent*
5				
10	3.3			0.8
15	9.4	6.1	185.0	2.4
20	22.1	12.7	135.0	5.6
25	44.0	21.9	97.5	11.2
30	77.8	33.8	76.8	19.8
35	126.6	48.8	62.7	32.2
40	193.3	66.7	52.7	49.1
45	281.0	87.7	45.4	71.4
50	392.9	111.9	42.4	100.0
55	532.1	139.2	35.4	135.5

TABLE 6

Volume of the encephalon (data of Jackson, '09)
(31 cases)

CROWN-HEEL LENGTH		ENCEPHALON VOLUME			NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean	
cm.	*cm.*	*cc.*	*cc.*	*cc.*	
0 to 5	1.8	0.4	0.25	0.18	3
5 to 10	7.7	3.6	2.0	2.83	3
10 to 15	12.3	20.0	10.0	13.7	3
15 to 20	17.2	40.0	18.0	27.2	5
20 to 25	22.4	60.0	30.6	45.9	4
25 to 30	27.4	129.0	52.7	85.4	5
30 to 35	32.7	126.7	120.0	123.3	2
35 to 40	38.5	140.0	140.0	140.0	1
40 to 45	44.2	321.3	321.3	321.3	1
45 to 50	45.9	358.0	278.2	322.6	2
50 to 55	51.9	385.0	363.0	374.0	2

140 per cent for the 10-to-15-cm. interval. It descends rapidly to 75 per cent of the 25-to-30-cm. interval, and then more slowly to 40 per cent in the 50-to-55-cm. interval.

The percentage increment of the entire brain volume when calculated against age in fetal months (fig. 28, curve VI) is about 580 per cent in the fourth month, descending to 22 per cent in the tenth month.

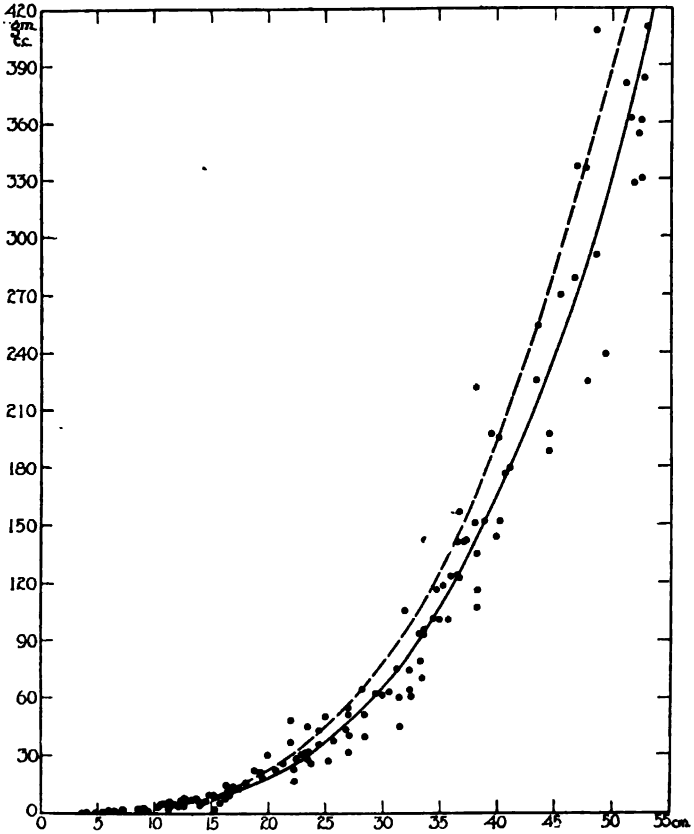

Fig. 3 Field graph and curve of the growth in weight and volume of the encephalon in fetal life (the curve of growth taken from brain weights reported in the literature). Abscissa: total body length in cm. Ordinate: entire brain weight and volume in grams (cc.). Individual cases are indicated by solid dots (for weight). *I*, curve of encephalon volume drawn to the formula: $Y = (0.125X)^{3.16} + 1.5$. ——— (Data from tables 3 and 4.) *II*, curve of encephalon weight based upon data from the literature and drawn to the formula: $Y = (0.13X)^{3.19} + 1.0$ . . . . . (Data from tables 5 and 6.)

Growth of the cerebrum

The growth of the cerebral hemispheres is portrayed by figures 3 to 9, inclusive, and figures 37 and 38, and is shown numerically in tables 3 to 16, inclusive. It may be expressed by the empirical formula:

$$\text{Volume of the cerebrum (cc.)} = (0.12\ (\text{C H length cm.}))^{3.19}$$

TABLE 7

Volume of the right hemisphere

Formula: Right hemisphere volume (cc.) = $(0.1 \text{ crown-heel length (cm.)})^{3.18}$

(115 cases)

CROWN-HEEL LENGTH		RIGHT HEMISPHERE VOLUME			CALCULATED RIGHT HEMISPHERE VOLUME	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5							
5 to 10							
10 to 15	12.5	4.2	1.6	2.6	2.0	−0.6	12
15 to 20	16.9	10.6	2.1	6.0	5.2	−0.8	14
20 to 25	22.6	21.8	9.3	14.2	12.8	−0.4	19
25 to 30	27.1	32.7	12.4	21.8	22.7	+0.9	12
30 to 35	32.6	73.1	21.1	39.2	40.4	+1.2	17
35 to 40	37.2	109.3	48.7	65.8	61.1	−4.7	16
40 to 45	42.5	126.6	67.2	94.6	92.6	−2.0	10
45 to 50	48.0	191.5	102.9	139.0	135.6	−3.4	7
50 to 55	52.2	185.3	148.0	166.0	176.4	+10.4	8

TABLE 8

Calculated volume of the right cerebral hemisphere at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	VOLUME OF RIGHT CEREBRAL HEMISPHERE	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cc.*	*cm.*	*per cent*	*per cent*
5				
10	1.0			0.6
15	3.6	2.6	260.0	2.3
20	8.8	5.2	144.0	5.7
25	17.6	8.8	100.0	11.4
30	31.1	13.5	76.6	20.2
35	50.5	19.4	62.3	32.7
40	76.4	25.9	51.2	49.5
45	110.8	34.4	45.0	71.8
50	154.2	43.4	39.2	100.0
55	207.7	53.5	34.7	134.5

The absolute volume of the right and of the left hemispheres (figs. 4 and 5) shows no marked differences—the minor distinctions between the two falling within the margin of experimental error.

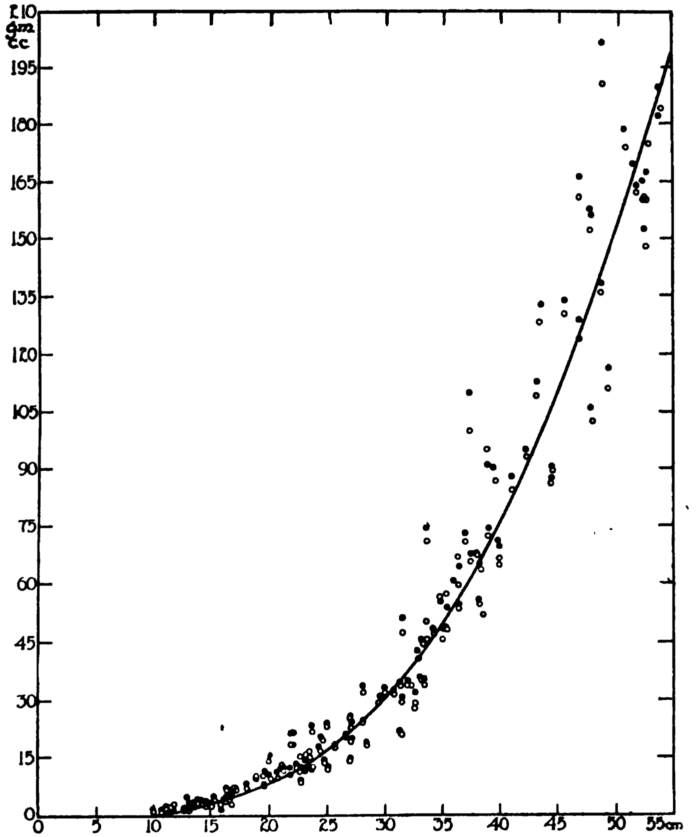

Fig. 4 Field graph and curve of the growth in weight and volume of the right cerebral hemisphere in fetal life. Abscissa: total body length in cm. Ordinate: right hemisphere weight and volume in grams (cc.). Individual cases are indicated by solid dots (for weight) and by circles (for volume). Curve drawn to the formula: $Y = (0.1X)^{3.13}$. (Data from tables 7 and 8.)

The absolute volume curve of the hemispheres shows the same concave form as the volume of the central nervous ststem (fig. 2). At 15 cm. (C H) the hemispheres are 1.8 cc. in volume, while in fetuses of 25 to 30 cm. (C H) they have reached an average volume of about 32 cc. After this time the volume curve increases more rapidly, attaining the average of about 300 cc. at 50 cm. (C H).

When examined in relation to age (fig. 34, curve II) the absolute volume of the right cerebral hemisphere is found to be 2 cc.

TABLE 9

Volume of the left cerebral hemisphere

Formula: Volume of the left cerebral hemisphere (cc.) = (0.105 crown-heel length (cm.))$^{3.04}$

CROWN-HEEL LENGTH		OBSERVED VOLUME OF THE LEFT HEMISPHERE			CALCULATED VOLUME OF THE LEFT HEMISPHERE	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5							
5 to 10							
10 to 15	12.5	4.4	1.3	2.6	2.3	−0.3	12
15 to 20	16.9	10.5	2.3	6.0	5.7	−0.3	14
20 to 25	22.4	20.0	10.2	14.8	13.5	−0.3	16
25 to 30	27.1	30.0	13.0	21.7	24.0	+2.3	13
30 to 35	32.8	50.0	21.0	38.2	42.9	+4.7	18
35 to 40	37.2	89.6	46.8	64.1	62.9	−1.2	16
40 to 45	42.5	110.7	67.0	92.2	94.4	+2.2	10
45 to 50	48.0	188.9	98.5	138.0	136.6	−1.4	7
50 to 55	52.2	192.0	142.0	170.0	176.2	+6.2	8

TABLE 10

Calculated volume of left cerebral hemisphere at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	VOLUME OF LEFT CEREBRAL HEMISPHERE	INCREMENT IN EACH 5-CM. INTERVAL OF CROWN-HEEL LENGTH		RATIO TO NEW-BORN
cm.	*cc.*	*cc.*	*per cent*	*per cent*
5				
10	1.2			0.8
15	4.0	2.8	233.0	2.6
20	9.6	5.6	140.0	6.2
25	18.8	9.2	96.0	12.1
30	32.8	14.0	74.5	21.2
35	52.5	19.7	60.0	33.9
40	78.3	25.8	49.1	50.6
45	111.2	32.9	42.0	71.9
50	154.9	43.7	39.2	100.0
55	200.3	45.4	29.3	129.2

at the beginning of the third month, and this rises at first slowly and then rapidly to about 150 cc. at birth.

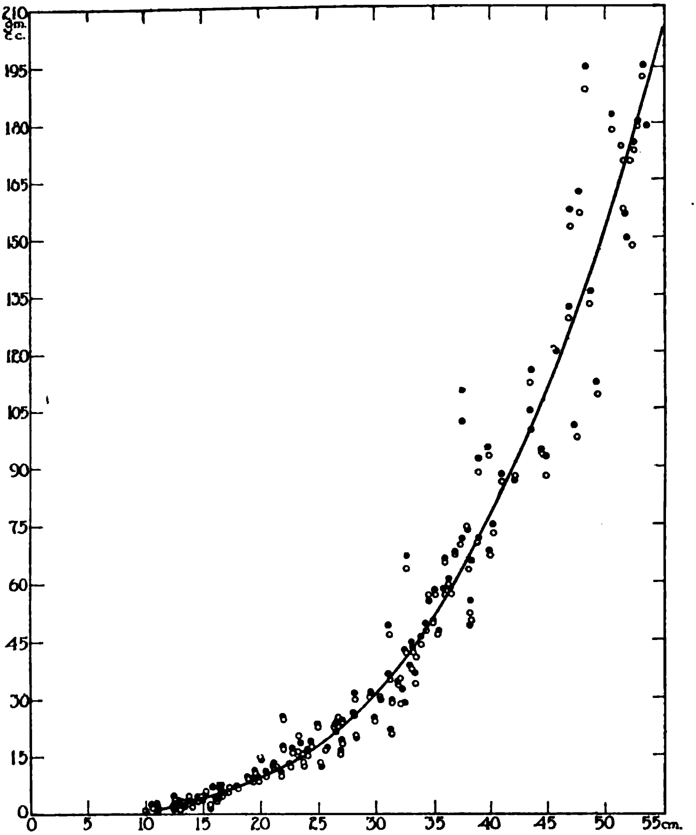

Fig. 5 Field graph and curve of the growth in weight and volume of the left cerebral hemisphere in fetal life. Abscissa: total body length in cm. Ordinate: left hemisphere weight and volume in grams (cc.). Individual cases indicated by solid dots (for weight) and by circles (for volume). Curvedrawn to the formula: $Y = (0.105X)^{3.04}$. (Data from tables 9 and 10.)

The percentage increment of the hemispheres (fig. 26, curve VI) approximates that of the entire brain. It is about 265 per cent for the interval between 10 and 15 cm. (C H) length and steadily declines from this value until it reaches the level of 35 per cent for the 50-to-55-cm. (C H) interval (birth).

The percentage increment of the hemispheres, when calculated by fetal months (fig. 28, curve V), shows an approximate rate of growth of 600 per cent in the fourth fetal month. This rate descends rapidly at first, and then more slowly to about 22 per cent in the tenth fetal month.

TABLE 11

Volume of both cerebral hemispheres

Formula: Volume of both cerebral hemispheres (cc.) = (0.12 crown-heel length (cm.))$^{3.19}$

(115 cases)

CROWN-HEEL LENGTH		OBSERVED VOLUME OF BOTH HEMISPHERES			CALCULATED VOLUME OF BOTH HEMISPHERES	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5							
5 to 10							
10 to 15	12.5	8.6	2.2	5.2	3.65	−1.55	12
15 to 20	16.9	20.5	4.8	12.2	9.5	−2.7	14
20 to 25	22.4	46.2	18.0	29.4	22.9	−6.5	16
25 to 30	27.1	62.5	25.4	46.6	43.0	−3.6	12
30 to 35	32.8	137.1	56.5	76.1	79.1	+3.0	18
35 to 40	37.2	210.8	95.5	131.4	118.2	−13.2	17
40 to 45	42.3	239.3	134.2	184.8	178.1	−6.7	11
45 to 50	48.0	380.4	201.2	277.0	266.5	−10.5	7
50 to 55	52.2	377.3	302.0	334.4	348.3	−13.9	8

TABLE 12

Calculated volume of both cerebral hemispheres at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	VOLUME OF BOTH CEREBRAL HEMISPHERES	INCREMENT IN EACH 5-CM. INTERVAL		RATIO OF NEW-BORN
cm.	*cc.*	*cc.*	*per cent*	*per cent*
5				
10	1.79			0.6
15	6.52	4.73	264.0	2.1
20	16.33	9.81	150.0	5.4
25	33.27	16.94	103.0	10.8
30	59.51	26.24	78.8	19.6
35	97.31	37.80	63.5	32.1
40	149.0	51.69	53.2	49.1
45	216.9	69.7	45.5	71.5
50	303.6	86.7	40.0	100.0
55	411.2	107.6	34.5	135.0

The per cent which the volume of both hemispheres forms of the entire brain volume (fig. 7) reflects the relative growth of the other brain parts. The cerebral hemispheres form only from

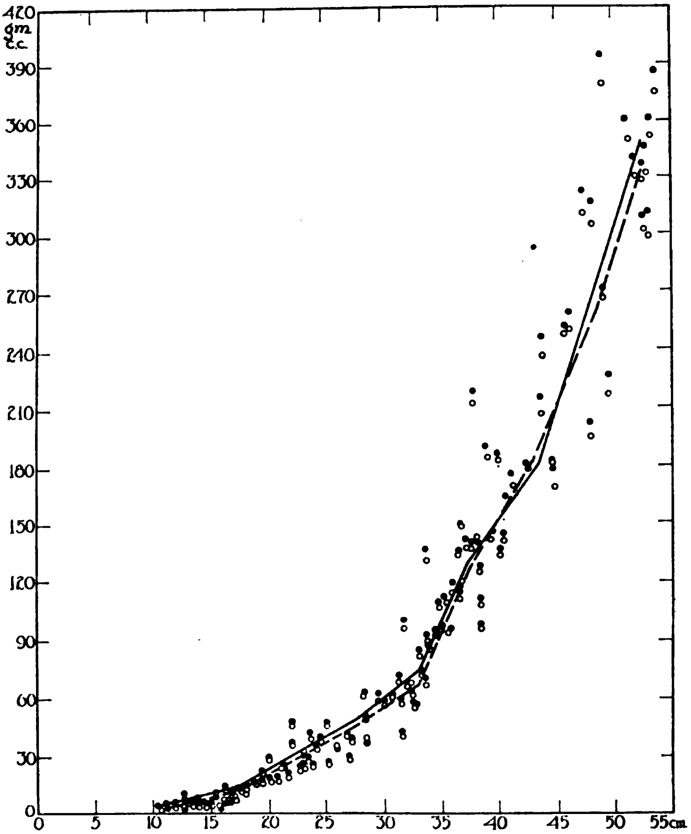

Fig. 6 Field graph and curve of the growth in weight and volume of both cerebral hemispheres in fetal life. Abscissa: total body length in cm. Ordinate: hemispheres weight and volume in grams (cc.). Individual cases indicated by solid dots (for weight) and by circles (for volume). Curve drawn to the formula: $Y = (0.12X)^{3.19}$. (Data from tables 11 and 12.)

88 to 90 per cent of the entire brain volume in the third fetal month. This proportion increases rapidly to between 94 and 95 per cent during the sixth fetal month, but after this time it descends to about 91.5 per cent at birth. This decline is due mainly to the tremendous relative growth of the cerebellum.

The two linear measurements of the cerebral hemispheres (the fronto-occipital and the temporal diameters) also furnish some information concerning the growth of this part of the brain. The fronto-occipital diameter is a very constant measure, due perhaps to its close conformance to the skull and to the fact that it is not affected greatly by the torsion of the brain parts or of the brain axis during growth. Its reliability has justified its use to some extent as a basic measurement.

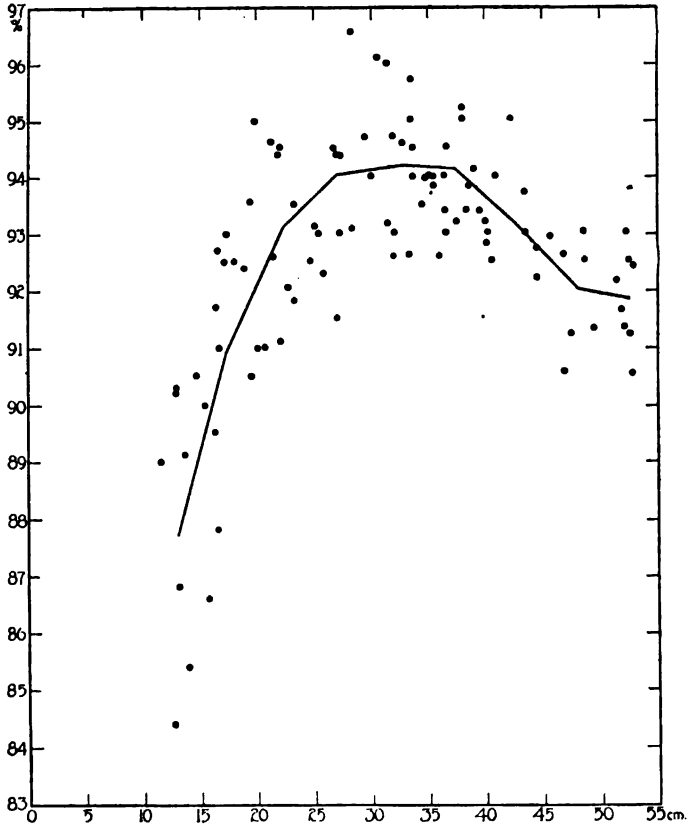

Fig. 7 Field graph and curve (connecting each 5-cm. crown-heel interval) of the per cent which the volume of both cerebral hemispheres forms of the encephalon volume. Abscissa: total body length in cm. Ordinate: hemisphere volume in per cent of the encephalon volume. Individual cases indicated by solid dots. (Data from table 40.)

The absolute fronto-occipital diameter (fig. 8) when plotted to the crown-heel length is a straight line ascending from 2 cm. at 10 cm. (C H) to 9 cm. at 50 cm. (C H). Its empirical formula is:

Fronto-occipital diameter (cm.) = 0.175 CH body length (cm.)
+ 0.25

TABLE 13

Fronto-occipital diameter

Formula: Fronto-occipital diameter (cm.) = .175 crown-heel length (cm.) + .25
(151 cases)

CROWN-HEEL LENGTH		OBSERVED FRONTO-OCCIPITAL DIAMETER			CALCULATED FRONTO-OCCIPITAL DIAMETER	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5	4.0	1.1	0.7	0.9	0.9	0	3
5 to 10	7.1	2.0	1.2	1.6	1.5	−0.1	10
10 to 15	12.3	2.7	1.4	2.3	2.4	+0.1	21
15 to 20	16.7	3.3	2.3	3.2	3.2	0	15
20 to 25	22.6	4.9	3.6	4.3	4.2	−0.1	21
25 to 30	27.0	6.5	4.4	5.1	5.0	−0.1	16
30 to 35	32.6	7.0	5.1	6.0	6.0	0	19
35 to 40	37.1	7.7	6.3	6.8	6.7	−0.1	19
40 to 45	42.3	8.4	7.2	7.8	7.6	−0.2	11
45 to 50	48.2	9.3	7.5	8.6	8.7	+0.1	8
50 to 55	52.2	10.0	8.0	9.2	9.4	+0.2	8

TABLE 14

Calculated fronto-occipital diameter at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	FRONTO-OCCIPITAL DIAMETER	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5	1.125			12.5
10	2.000	0.875	78.0	22.2
15	2.875	0.875	43.7	31.9
20	3.750	0.875	30.3	41.6
25	4.625	0.875	23.3	51.4
30	5.500	0.875	18.9	61.1
35	6.375	0.875	15.9	70.8
40	7.250	0.875	13.6	80.5
45	8.125	0.875	12.1	90.3
50	9.000	0.875	10.8	100.0
55	9.875	0.875	9.7	109.8

The absolute fronto-occipital diameter when considered in relation to age (fig. 32, curve I) is about 1.3 cm. in the middle of the third fetal month and increases at first rapidly and then more slowly to 9 cm. at birth.

The percentage increment of the fronto-occipital length for 5-cm. intervals of body length (fig. 25, curve I) gradually declines from about 80 per cent in the 5-to-10-cm. interval to about 10 per cent in the 50-to-55-cm. interval.

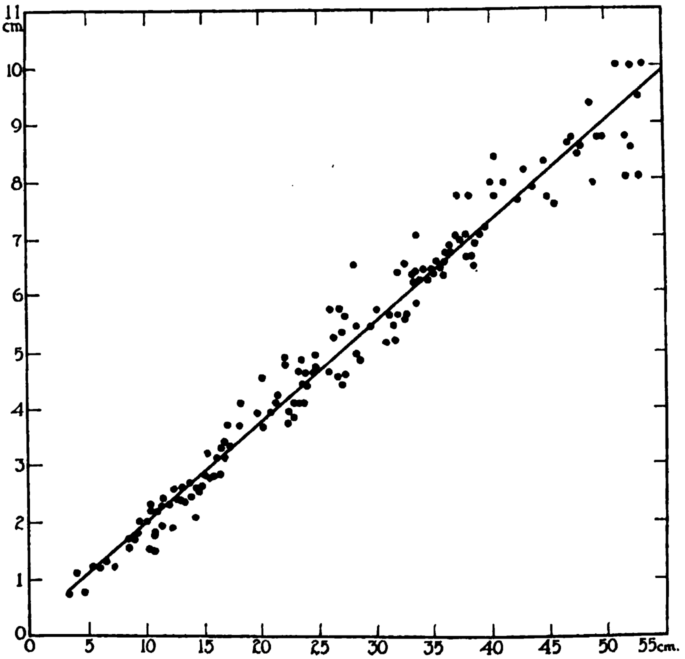

Fig. 8 Field graph and curve of the growth of the cerebral hemispheres in fetal life as shown by the fronto-occipital diameter. Abscissa: total body length in cm. Ordinate: fronto-occipital diameter in cm. Individual cases indicated by solid dots. Curve drawn to the formula. $Y = 0.175X + 0.25$. (Data from tables 13 and 14.)

The percentage increment of the fronto-occipital length, when calculated for fetal months (fig. 27, curve I), shows an approximate rate of growth of 150 per cent in the third fetal month. This descends rapidly to 31 per cent in the fifth month and gradually to 9.5 per cent in the last fetal month.

The linear measurement from the frontal to the occipital pole indicates therefore a steady absolute cerebral growth in the anteroposterior axis (when compared to crown-heel length) and a constant diminution of the rate of growth (when compared to time).

TABLE 15

Temporal diameter

Formula: Temporal diameter (cm.) = 0.138 crown-heel length (cm.) + 0.3 (141 cases)

CROWN-HEEL LENGTH		OBSERVED TEMPORAL DIAMETER			CALCULATED TEMPORAL DIAMETER	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5	3.9	1.0	0.7	0.85	0.85	0	4
5 to 10	8.1	2.0	1.1	1.45	1.4	−0.03	7
10 to 15	12.4	3.5	1.5	2.1	2.0	−0.1	19
15 to 20	16.6	3.4	1.8	2.6	2.6	0	15
20 to 25	22.6	4.2	2.6	3.3	3.4	+0.1	21
25 to 30	27.0	4.6	3.2	4.1	4.0	−0.1	15
30 to 35	32.6	5.0	3.8	4.5	4.8	+0.3	16
35 to 40	37.1	6.8	4.6	5.5	5.4	−0.1	18
40 to 45	42.3	6.7	5.6	6.2	6.1	−0.1	11
45 to 50	48.2	7.2	6.6	6.7	6.95	+0.25	8
50 to 55	52.2	10.4	6.9	7.9	7.5	−0.4	7

TABLE 16

Calculated temporal diameter at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	TEMPORAL DIAMETER	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5	0.99			13.7
10	1.68	0.69	69.7	23.4
15	2.37	0.69	41.1	32.9
20	3.06	0.69	29.1	42.6
25	3.75	0.69	22.5	52.1
30	4.44	0.69	18.4	61.6
35	5.13	0.69	15.5	71.3
40	5.82	0.69	13.4	81.0
45	6.51	0.69	11.8	90.4
50	7.20	0.69	10.6	100.0
55	7.89	0.69	9.6	109.5

The curve of absolute temporal diameter (fig. 9) is also a straight line when based on crown-heel length. Starting at about 1 cm. at the 5 cm. (C H), it increases steadily to about 72 cm. at 50 cm. (C H). Its empirical formula is:

Temporal diameter (cm.) = 0.138 C H body length (cm.) +0.3

When studied in relation to time (fig. 32, curve II), this diameter is found to be 1 cm. at the beginning of the third fetal month and to rise at first fairly rapidly and then more slowly to 7.2 cm. at birth.

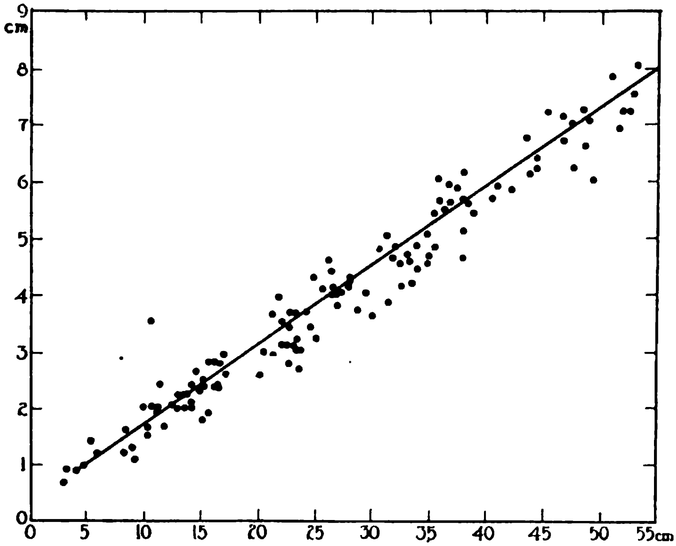

Fig. 9 Field graph and curve of the growth of the cerebral hemispheres in fetal life as shown by the temporal diameter. Abscissa: total body length in cm. Ordinate: temporal diameter in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = 0.138X + 0.3$. (Data from tables 15 and 16.)

The rate of growth of the temporal diameter (fig. 25, curve II) decreases steadily from 70 per cent for the 5-to-10-cm. interval to about 10 per cent for the 50-to-55-cm. interval.

The percentage increment of the temporal diameter, when calculated for fetal months (fig. 27, curve II), is approximately 70 per cent in the fourth fetal month and falls to about 35 per cent in the fifth month and to 9.2 per cent in the tenth month. Or, in other words, the transverse axis of the cerebral hemispheres shows a constant diminution in the rate of growth throughout the fetal period.

TABLE 17

Volume of the cerebellum

Formula: Volume of cerebellum (cc.) = .01 (.095 crown-heel length (cm.))$^{4.9}$ + 20.0

(114 cases)

CROWN-HEEL LENGTH		OBSERVED VOLUME OF CEREBELLUM			CALCULATED VOLUME OF CEREBELLUM	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5							
5 to 10							
10 to 15	12.8	0.5	0.1	0.3	0.5	+0.2	10
15 to 20	16.9	0.7	0.2	0.4	0.5	+0.1	14
20 to 25	22.6	2.0	0.5	0.9	0.6	−0.3	18
25 to 30	27.0	2.7	0.9	1.3	1.2	−0.1	13
30 to 35	32.7	4.0	1.0	2.4	2.8	+0.4	16
35 to 40	37.2	9.3	3.4	5.4	5.1	−0.3	17
40 to 45	42.3	11.5	5.7	8.9	9.3	+0.4	11
45 to 50	48.0	22.0	14.0	19.0	17.1	−2.0	7
50 to 55	52.2	26.0	18.0	21.3	25.7	+4.4	8

TABLE 18

Calculated cerebellum volume at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	CEREBELLUM VOLUME	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cc.*	*cc.*	*per cent*	*per cent*
5				
10	0.20			1.0
15	0.28	0.08	40.0	1.3
20	0.43	0.15	53.6	2.1
25	0.89	0.46	107.0	4.3
30	1.89	1.00	112.0	9.1
35	3.80	1.91	100.1	18.2
40	7.13	3.33	87.8	34.1
45	12.60	5.47	76.8	60.3
50	20.90	8.30	65.8	100.0
55	33.40	12.50	59.8	160.0

Growth of the cerebellum

The growth of the cerebellum is portrayed by the graphs in figures 10 to 13, inclusive, and by the outline sketches in figure 38. The absolute volume of the cerebellum, when plotted against crown-heel body length (fig. 10), presents a concave volume curve expressed by the empirical formula:

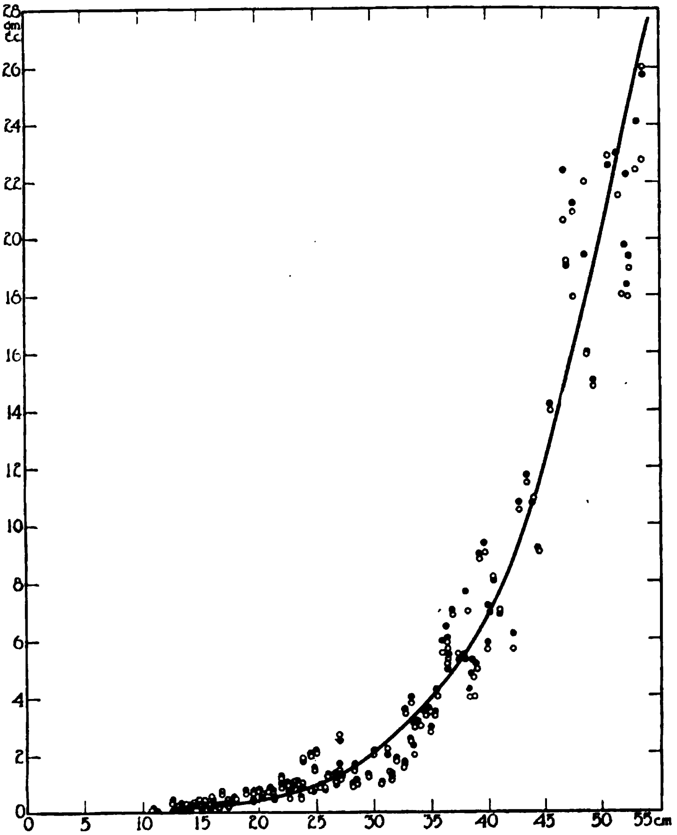

Fig. 10 Field graph and curve of the growth of the cerebellum in weight and volume in fetal life. Abscissa: total body length in cm. Ordinate: cerebellum weight and volume in grams (cc.). Individual cases indicated by solid dots (for weight) and by circles (for volume). Curve drawn to the formula: $Y = 0.01\ [(0.095X)^{4.9} + 20.0]$. (Data from tables 17 and 18.)

Volume of the cerebellum (cc.) = $0.01\ (0.095$ C H body length (cm.)$)^{4.9} + 20.0$

The cerebellum is not grossly visible before the fetus is about 10 cm. (C H) long. At 20 cm. (C H) its volume is about 0.4 cc., and this increases slowly to about 2 cc. at 30 cm. (C H). The absolute volume curve then turns sharply upward and rises very rapidly to 21 cc. at 50 cm. (C H).

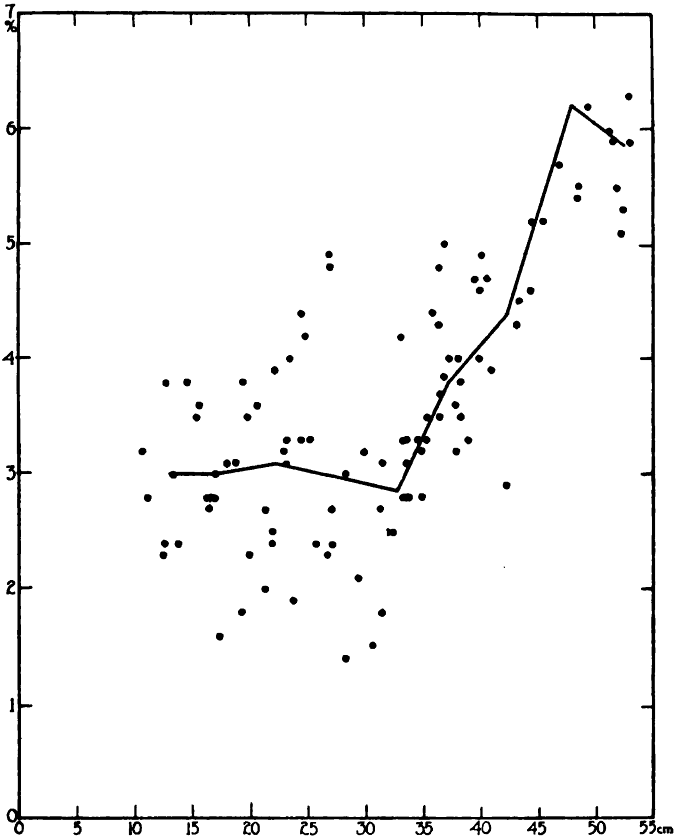

Fig. 11 Field graph and curve (connecting the average points of each 5-cm. crown-heel interval) of the per cent which the volume of the cerebellum forms of the encephalon volume. Abscissa: total body length in cm. Ordinate: cerebellum volume in per cent of entire brain volume. Individual cases indicated by solid dots. (Data from table 40.)

On the basis of time (figs. 34 and 35), the volume of the cerebellum is about 0.4 cc. at four fetal months and approximately

2.3 cc. at six fetal months. At this time it begins to enlarge rapidly, increasing almost ten-fold in the last four months of intra-uterine life and reaching a volume of 21 cc. at birth. This tremendous growth in volume in the last three or four months of fetal life, at a time when all other brain parts are growing far less rapidly, is a peculiar characteristic of the cerebellum.

The percentage increment of the cerebellum volume (fig. 26, curve VII) reflects the peculiarities of the curve of absolute volume. Starting at a comparatively low value, it rises to a peak of 112 per cent for the 25-to-30-cm. interval and descends to 60 per cent in the 50-to-55-cm. interval.

The percentage increment of the cerebellum volume, when calculated for time (fig. 28, curve IV), shows an approximate rate of growth of about 160 per cent in the fifth month, and then falls rapidly to 54 per cent for the tenth month.

The relative growth of the cerebellum is also illustrated by the per cent which it forms of the entire brain volume at various periods in fetal life (fig. 11). This value is, with slight variations, about 3 per cent until the middle of the sixth fetal month. At this time the tremendous growth of the cerebellum becomes an important factor in the total increase of the brain as a whole, and by birth it forms about 6 per cent of the entire brain volume.

The absolute length of the vermis cerebelli, when plotted to crown-heel body length (fig. 12), is expressed by the formula:

$$\text{Vermis cerebelli length (cm.)} = 0.01\ [(\text{C H length (cm.)})^{1.41} + 0.15]$$

It also portrays the great growth of this part of the brain in the last four fetal months. At 10 cm. (C H) the vermis cerebelli length is only about 0.4 cm. It ascends in a very shallow curve to 2.6 cm. at 50 cm. (C H).

The absolute length of the vermis cerebelli when calculated for fetal months (fig. 31, curve I) rises in practically a straight line from 0.4 cm. at the beginning of the fourth month to 2.64 cm. at birth.

The rate of growth of the vermis cerebelli length (fig. 25, curve III) shows a gradual decrease from 50 per cent in the 10-to-15-cm. interval to 13 per cent at the 50-to-55-cm. interval. The entire percentage increment curve, however, is much higher than any other percentage increment based upon a straight-line measurement (with the single exception of the vermis cerebelli height, fig. 25, curve IV).

TABLE 19

Length of the vermis cerebelli

Formula: Vermis cerebelli length (cm.) = .01 [(crown-heel length (cm.))$^{1.41}$ + 0.15]
(124 cases)

CROWN-HEEL LENGTH		LENGTH OF VERMIS CEREBELLI			CALCULATED LENGTH OF VERMIS CEREBELLI	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5							
5 to 10							
10 to 15	12.7	0.9	0.3	0.5	0.5	0.0	16
15 to 20	16.9	1.1	0.4	0.6	0.7	+0.1	14
20 to 25	22.5	1.2	0.6	0.9	1.0	+0.1	18
25 to 30	27.0	1.8	0.9	1.15	1.2	+0.05	14
30 to 35	32.8	1.7	1.1	1.5	1.5	0	16
35 to 40	37.1	2.6	1.3	1.8	1.8	0	18
40 to 45	42.2	2.5	1.7	2.1	2.1	0	12
45 to 50	48.2	2.7	2.2	2.5	2.5	0	8
50 to 55	52.2	3.4	2.5	2.7	2.8	+0.1	8

TABLE 20

Calculated vermis cerebelli length at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	VERMIS CEREBELLI LENGTH	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5				
10	0.41			15.5
15	0.61	0.20	49.0	23.1
20	0.83	0.22	36.1	31.5
25	1.08	0.25	30.2	40.9
30	1.36	0.28	25.9	51.6
35	1.65	0.29	21.3	62.6
40	1.96	0.31	18.8	74.3
45	2.29	0.33	16.8	86.8
50	2.64	0.35	15.3	100.0
55	2.99	0.35	13.3	113.2

The percentage increment of the vermis cerebelli length when calculated for fetal months (fig. 27, curve VIII) is approximately 85 per cent in the fifth month, descending at first swiftly and then more slowly to about 12.5 per cent in the tenth month.

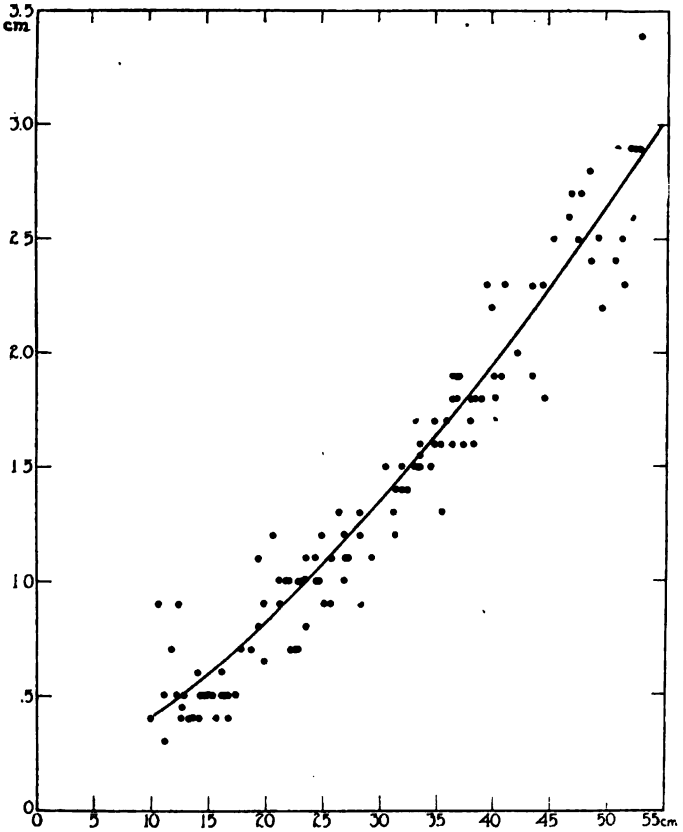

Fig. 12 Field graph and curve of the growth of the cerebellum in fetal life as shown by the vermis cerebelli length. Abscissa: total body length in cm. Ordinate: vermis cerebelli length in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = 0.01 (X^{1.41} + 0.15)$. (Data from tables 19 and 20.)

The absolute height of the vermis cerebelli when plotted against crown-heel body length (fig. 13) also forms a shallow curve, expressed empirically by the formula:

Vermis cerebelli height (cm.) = 0.01 (C H body length (cm.))$^{1.37}$

It is 0.23 cm. at 10 cm. (C H) and rises to about 2.1 cm. at 50 cm. (C H).

TABLE 21

Height of the vermis cerebelli

Formula: Vermis cerebelli height (cm.) = .01 (crown-heel length (cm.))$^{1.37}$

(122 cases)

CROWN-HEEL LENGTH		OBSERVED HEIGHT OF VERMIS CEREBELLI			CALCULATED HEIGHT OF VERMIS CEREBELLI	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5							
5 to 10							
10 to 15	12.7	0.6	0.3	0.4	0.3	−0.1	14
15 to 20	16.9	0.7	0.2	0.5	0.5	0	14
20 to 25	22.6	0.9	0.5	0.7	0.7	0	18
25 to 30	27.0	1.0	0.6	0.8	0.9	+0.1	14
30 to 35	32.8	1.4	0.8	1.1	1.2	+0.1	16
35 to 40	37.1	1.9	1.0	1.4	1.4	0	18
40 to 45	42.2	2.0	1.1	1.6	1.7	+0.1	12
45 to 50	48.2	2.5	1.6	2.0	2.0	0	8
50 to 55	52.2	2.8	1.6	2.2	2.2	0	8

TABLE 22

Calculated vermis cerebelli height at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	VERMIS CEREBELLI HEIGHT	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5				
10	0.23			10.8
15	0.41	0.18	78.1	19.2
20	0.61	0.20	48.8	28.6
25	0.82	0.21	34.4	38.5
30	1.06	0.24	29.2	49.8
35	1.31	0.25	23.6	61.5
40	1.57	0.26	19.8	73.7
45	1.84	0.27	17.2	86.3
50	2.13	0.29	15.8	100.0
55	2.42	0.29	12.0	113.7

The absolute height of the vermis cerebelli when calculated for age in fetal months (fig. 31, curve II) rises in practically a straight line from 0.23 cm. at the beginning of the fourth month to 2.1 cm. at birth.

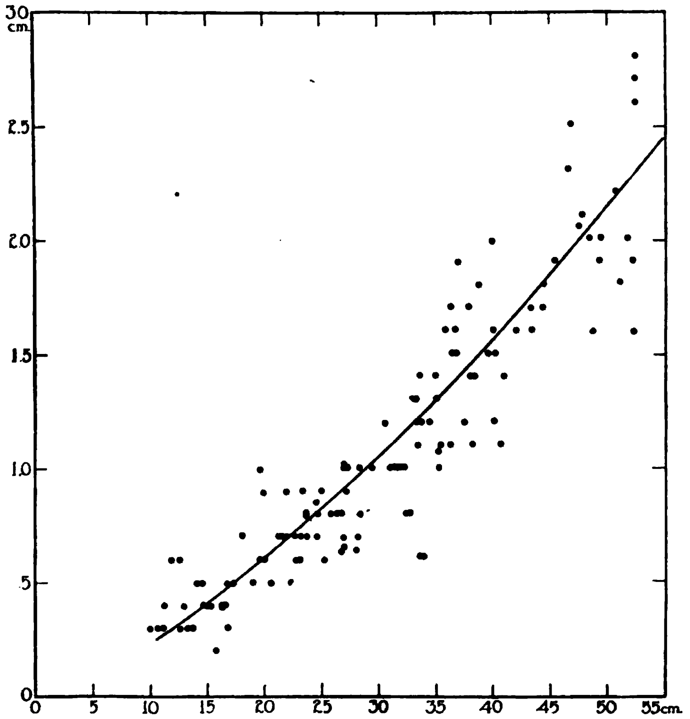

Fig. 13 Field graph and curve of the growth of the cerebellum in fetal life as shown by the vermis cerebelli height. Abscissa: total body length in cm. Ordinate: vermis cerebelli height in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = 0.01\ (X^{1.37})$. (Data from tables 21 and 22.)

The percentage increment of the vermis cerebelli height when calculated for 5-cm. intervals of crown-heel length (fig. 25, curve IV) is similar to that of the vermis cerebelli length except that it is somewhat greater at first and falls more rapidly.

The percentage increment of the vermis cerebelli height, when calculated for fetal months (fig. 27, curve IX), shows a rate of growth of about 126 per cent for the fourth month, falls to 58 per cent for the fifth month, and then descends steadily to about 13 per cent for the tenth month.

The growth of the cerebellum during the latter part of fetal life is also strikingly illustrated by the midsagittal sections shown in figures 37 and 38. In the third fetal month (figure 38, C) the cerebellum grows posteriorly and parallel to the pons and medulla; by the middle of the sixth fetal month (fig. 38, D, E, F) it assumes its characteristic shape and position in relation to the cerebral hemispheres. From the middle of the sixth fetal month to birth (fig. 38, G to I, inclusive) each succeeding tracing indicates a greater relative size in this portion of the brain.

It will be noted in this connection that the graphs of absolute growth of the cerebellum in both of the linear dimensions resemble volume curves much more closely than does the graphic expression of any other lineal dimensions of the nervous system.

Growth of the pons and medulla

The growth of the pons and medulla (fig. 14) presents a typical volume curve having the empirical formula:

$$\text{Pons and medulla volume (cc.)} = 0.01\ [(0.2\ \text{C H body length (cm.)})^{2.67} + 20.0]$$

At 10 cm. (C H) their volume is about 0.3 cc., by 30 cm. (C H) it is 1.4 cc., and at birth (50 cm. C H) it is approximately 5 cc. When calculated for age in fetal months (fig. 35, curve II), their volume is 0.2 cc. at three months and 1.4 cc. at six months. From this time it rises steadily to about 5 cc. at birth.

The percentage increment of the volume (fig. 26, curve VIII) is approximately 50 per cent for the 10-to-15-cm. (C H) interval and rises to about 56 to 57 per cent for the interval between 15 to 20 cm. It then descends steadily to about 27 per cent from 50 to 55 cm. (C H).

The percentage increment of the pons and medulla volume as calculated for fetal months (fig. 28, curve II) shows a rate of growth of about 96 per cent for the fourth month, and then descends steadily to about 27.5 per cent for the last month of prenatal life.

One of the most interesting facts concerning the prenatal growth of the pons and medulla is the per cent of the entire brain volume which they form during fetal life (fig. 15 and table 40). In the middle of the fourth fetal month the pons and medulla make up 5.5 per cent of the entire brain volume, at 5 months they

TABLE 23

Volume of the pons and medulla

Formula: Pons and medulla volume (cc.) $= .01\ [(.2 \text{ crown-heel length (cm.)})^{2.67} + 20]$

(112 cases)

CROWN-HEEL LENGTH		OBSERVED PONS AND MEDULLA VOLUME			CALCULATED PONS AND MEDULLA VOLUME	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5							
5 to 10							
10 to 15	12.6	0.5	0.2	0.3	0.3	0	11
15 to 20	16.9	0.7	0.15	0.4	0.5	+0.1	14
20 to 25	22.5	1.0	0.4	0.8	0.8	0	16
25 to 30	27.0	1.4	0.5	0.9	1.1	+0.2	13
30 to 35	32.7	2.1	0.9	1.5	1.7	+0.2	17
35 to 40	37.0	3.2	1.6	2.4	2.3	−0.1	16
40 to 45	42.3	3.9	2.5	3.1	3.2	+0.1	11
45 to 50	48.0	5.5	3.7	4.3	4.4	+0.1	6
50 to 55	52.2	6.3	4.5	5.2	5.4	+0.2	8

TABLE 24

Calculated pons and medulla volume at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	PONS AND MEDULLA VOLUME	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cc.*	*cc.*	*per cent*	*per cent*
5				
10	0.26			5.3
15	0.39	0.13	50.0	8.0
20	0.61	0.22	56.5	12.5
25	0.94	0.33	54.1	19.3
30	1.40	0.46	49.0	28.7
35	2.01	0.61	43.5	41.2
40	2.78	0.77	38.3	57.0
45	3.73	0.95	34.2	76.4
50	4.88	1.15	30.8	100.0
55	6.23	1.35	27.7	128.0

form only about 2.7 per cent, and from that time on to birth they gradually decrease in relative volume, so that they form only 1.5 per cent of the entire brain volume in the new-born. This relative decline is clearly due to the great increase in the absolute volume of the cerebral hemispheres and of the cerebellum during the last half of fetal life.

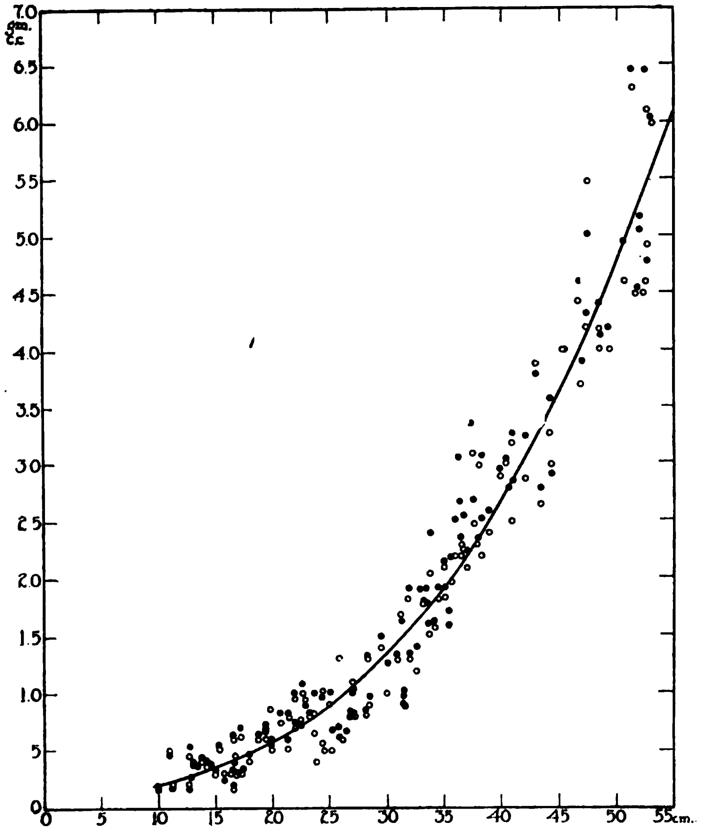

Fig. 14 Field graph and curve of the growth of the pons and medulla in weight and volume in fetal life. Abscissa: total body length in cm. Ordinate: pons and medulla weight and volume in grams (cc.). Individual cases indicated by solid dots (for weight) and by circles (for volume). Curve drawn to the formula: $Y = 0.01\,[(0.2X)^{2.67} + 20.0]$. (Data from tables 23 and 24.)

The pons length also shows some interesting changes in the course of fetal life. The graph of absolute pons length plotted against total body length (fig. 16) is practically a straight line having the formula:

Length of pons (cm.) = 0.0263 C H body length (cm.) + 0.16

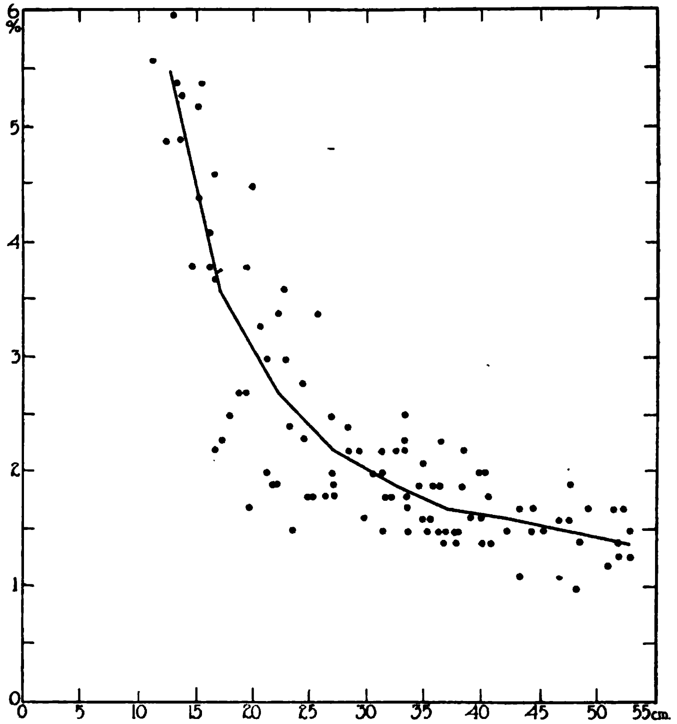

Fig. 15 Field graph and curve (connecting the average points of each 5-cm. crown-heel interval) of the per cent which the volume of the pons and medulla forms of the encephalon volume. Abscissa: total body length in cm. Ordinate: pons and medulla volume in per cent of the entire brain volume. Individual cases indicated by solid dots. (Data from table 40.)

The length increases steadily from 0.42 cm. at 10 cm. (C H) to about 1.53 cm. at birth (50 cm. C H).

When plotted against time, the pons length increases rather rapidly from the third to the beginning of the sixth month, and then grows more slowly at a uniform rate until birth.

The percentage increment of the pons length against intervals of growth in body length (fig. 25, curve V) starts at 30 per cent between 10 and 15 cm. (C H) and falls steadily but slowly to 9.8 per cent in the 50-to-55-cm. interval.

The percentage increment of the pons length as calculated for fetal months (fig. 27, curve III) shows a rate of growth of about

TABLE 25

Pons length

Formula: Pons length (cm.) = 0.0263 crown-heel length (cm.) + 0.16 (124 cases)

CROWN-HEEL LENGTH		OBSERVED PONS LENGTH			CALCULATED PONS LENGTH	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5							
5 to 10							
10 to 15	12.2	0.6	0.3	0.5	0.5	0	18
15 to 20	16.7	0.8	0.5	0.6	0.6	0	13
20 to 25	22.6	0.9	0.7	0.8	0.8	0	18
25 to 30	27.0	1.1	0.6	0.9	0.9	0	13
30 to 35	32.8	1.2	0.9	1.0	1.0	0	16
35 to 40	37.1	1.5	1.0	1.2	1.1	—0.1	18
40 to 45	42.2	1.4	1.0	1.3	1.3	0	12
45 to 50	48.2	1.6	1.2	1.35	1.4	−0.05	8
50 to 55	52.2	1.7	1.3	1.5	1.5	0	8

TABLE 26

Calculated pons length at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	PONS LENGTH	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5	0.29			
10	0.42	0.13+	44.8	28.7
15	0.55	0.13+	30.0	37.6
20	0.68	0.13+	24.8	46.5
25	0.81	0.13+	19.2	55.4
30	0.94	0.13+	16.1	64.3
35	1.08	0.13+	13.9	73.3
40	1.21	0.13+	12.2	82.3
45	1.34	0.13+	11.8	91.2
50	1.47	0.13+	9.8	100.0
55	1.60	0.13+	8.9	108.8

75 per cent in the third month and descends steadily to approximately 7 per cent in the tenth month.

There is no doubt that the pons and medulla form a large part of the brain in early fetal life. Figures 38, a, b, c, and d, substantiate the percentage curve (fig. 18). They show that the pons and medulla form a very large portion of the entire brain volume at this time. By the middle of the third fetal month (fig. 38, b) fully one-third of the brain, as it is seen in midsagittal section, is formed by the pons and medulla. In the fourth and fifth months (figs. 38, b, c, d, and e) the pons and medulla become relatively smaller.

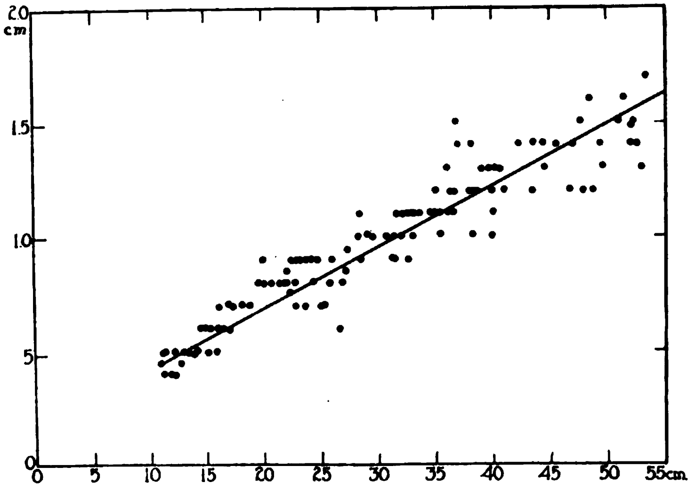

Fig. 16 Field graph and curve of the growth of the pons and medulla in fetal life, as shown by the pons length. Abscissa: total body length in cm. Ordinate: pons length in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = 0.0263X + 0.16$. (Data from tables 25 and 26.)

Growth of the midbrain

A consideration of the colliculi and the midbrain does not lead to quite such clean-cut results as does the study of the other brain parts. The midbrain, as it was prepared for the volume and weight determinations, included not only the colliculi above the iter, but also a portion of the brain stem below it.

The absolute volume of the midbrain when plotted against body length (fig. 17) presents a shallow curve and has the empirical formula:

$$\text{Volume of midbrain (cc.)} = 0.01\ [(0.168\ \text{C H length (cm.)})^{2.56} + 12.0]$$

TABLE 27

Volume of the midbrain

Formula: Midbrain volume (cc.) = $.01\ [\ (.168\ \text{crown-heel length (cm.)})^{2.56} + 12]$

(109 cases)

CROWN-HEEL LENGTH		OBSERVED MIDBRAIN VOLUME			CALCULATED VOLUME OF MIDBRAIN	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5							
5 to 10							
10 to 15	12.9	0.3	0.1	0.2	0.2	0	9
15 to 20	16.9	0.4	0.2	0.3	0.3	0	14
20 to 25	22.5	0.8	0.3	0.5	0.4	−0.1	17
25 to 30	27.0	0.9	0.4	0.6	0.6	0	13
30 to 35	32.7	1.4	0.4	0.8	0.9	+0.1	16
35 to 40	37.3	1.7	0.8	1.4	1.2	−0.2	14
40 to 45	42.3	2.2	1.2	1.6	1.6	0	11
45 to 50	48.0	3.1	1.5	2.4	2.2	−0.2	7
50 to 55	52.2	3.0	1.8	2.4	2.7	+0.3	8

TABLE 28

Calculated midbrain volume at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	MIDBRAIN VOLUME	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cc.*	*cc.*	*per cent*	*per cent*
5				
10	0.16			6.6
15	0.23	0.07	43.7	9.4
20	0.34	0.11	47.8	13.9
25	0.51	0.17	50.0	20.9
30	0.75	0.24	47.0	30.7
35	1.05	0.30	40.0	43.0
40	1.43	0.38	36.2	58.5
45	1.89	0.46	32.0	77.4
50	2.44	0.55	29.1	100.0
55	3.12	0.68	27.8	128.0

At 13 cm. (C H) the absolute midbrain volume is about 0.2 cc., and this steadily rises to 0.75 cc. at 30 cm. (C H). From this point the absolute volume increases at a faster pace to about 2.5 cc. at 50 cm. (C H).

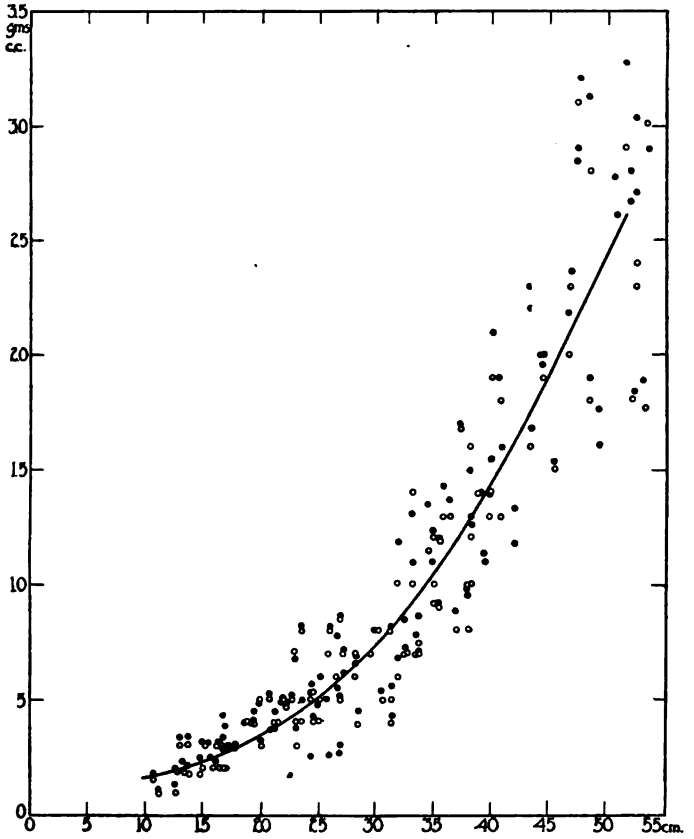

Fig. 17 Field graph and curve of the growth of the midbrain in weight and volume in fetal life. Abscissa: total body length in cm. Ordinate: midbrain weight and volume in grams (cc.). Individual cases indicated by solid dots (for weight) and by circles (for volume). Curve drawn to the formula: $Y = 0.01 [(0.168X)^{3.56} + 12.0]$. (Data from tables 27 and 28.)

The volume of the midbrain, when calculated for age in fetal months (fig. 35, curve III), is about 0.15 cc. at the third month and increases to about 0.8 cc. at six months. Thereafter it grows slowly to about 2.5 cc. at birth.

The percentage increment of the midbrain volume, when calculated for 5-cm. intervals of crown-heel length (fig. 26, curve IX), is about 45 per cent for the 10-to-15-cm. interval. It rises slightly at the 20-to-25-cm. interval and descends to 30 per cent for the 50-to-55-cm. interval.

The percentage increment of the midbrain volume as calculated for fetal months (fig. 28, curve III) is approximately 81 per cent in the fourth month and descends to about 25 per cent in the last fetal month.

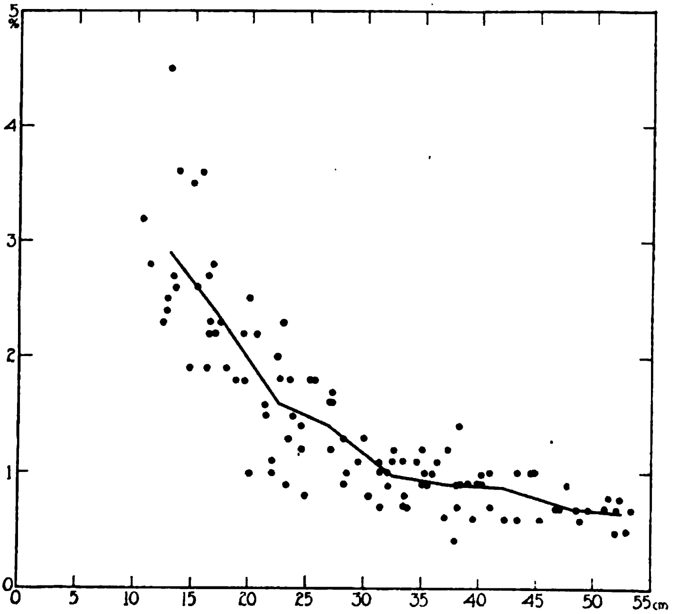

Fig. 18 Field graph and curve (connecting the average points of each 5-cm. crown-heel interval) of the per cent which the midbrain volume forms of the encephalon volume. Abscissa: total body length in cm. Ordinate: mid-brain volume in per cent of the encephalon volume. Individual cases indicated by solid dots. (Data from table 40.)

The slow growth of the midbrain is reflected in the per cent which this brain part forms of the entire brain volume (figure 18 and table 40). Beginning at 2.9 per cent at three months, it steadily declines to but 0.7 per cent of the entire brain volume at birth.

The length of the colliculi is not a true index of the midbrain growth in early fetal life, and its significance as a measure of growth of that portion of the mesencephalon below the iter is particularly questionable. In some fetuses of three to four months a sharp line of demarcation between the superior colliculi and the thalamencephalon may be present, while in other specimens of the same age no line of separation can be distinguished.

This conclusion is supported by evidence shown in figures 36, a, b, c. Figures 36, a, and 36, b, of specimens prior to the third fetal month show no colliculi; figure 36, c, shows colliculi well marked off and relatively larger than in a new-born specimen.

The curve of the absolute length of the colliculi, when plotted against body length (fig. 19), is a straight line. It starts at 0.7 cm. at 15 cm. (C H) and rises to 1.22 cm. in length at 50 cm. (C H). It may be expressed by the empirical formula:

$$\text{Length of colliculi (cm.)} = 0.015 \text{ C H body length (cm.)} + 0.47$$

The growth of the colliculi in absolute length when plotted against time (fig. 33, curve VI) approaches a straight line, although the rate of growth is more rapid in the fourth and fifth months than in the last four fetal months.

Growth of the spinal cord

The growth of the spinal cord resembles that of the brain and particularly that of the pons and medulla. The absolute volume of the spinal cord plotted against crown-heel length (fig. 21) is a very shallow but typical volume curve, which may be expressed by the empirical formula:

$$\text{Volume of the spinal cord (cc.)} = 0.01 \left[(0.17 \text{ C H length (cm.)})^{2.57} + 11.0\right]$$

The absolute volume at 15 cm. (C H) is approximately 0.22 cc. The curve rises steadily until it reaches about 1 cc. at 35 cm. (C H). From this point it proceeds upward at a sharper pitch, reaching about 2.5 cc. at 50 cm. (C H).

The growth in absolute volume against time (fig. 35, curve IV) corresponds almost exactly with that of the midbrain and shows a fairly rapid rate of absolute growth from the third to the beginning of the fifth month and a slower and more regular growth thereafter.

The data of Jackson ('09) (table 35) show a uniformly higher average for the absolute spinal cord volumes. His small fetuses

TABLE 29

Length of the colliculi

Formula: Colliculi length (cm.) = .015 crown-heel length (cm.) + .47.

(117 cases)

CROWN-HEEL LENGTH		OBSERVED LENGTH OF THE COLLICULI			CALCULATED LENGTH OF THE COLLICULI	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5							
5 to 10							
10 to 15	13.0	0.9	0.5	0.66	0.66	0	11
15 to 20	16.9	0.9	0.5	0.74	0.73	−0.01	14
20 to 25	22.5	1.0	0.7	0.80	0.81	+0.01	18
25 to 30	26.9	1.0	0.7	0.90	0.87	−0.03	12
30 to 35	32.8	1.7	0.8	0.99	0.96	−0.03	16
35 to 40	37.1	1.1	0.9	0.98	1.03	+0.05	18
40 to 45	42.2	1.2	1.0	1.10	1.10	0	12
45 to 50	48.3	1.4	1.1	1.23	1.20	−0.03	8
50 to 55	52.2	1.3	1.1	1.20	1.25	+0.05	8

TABLE 30

Calculated length of the colliculi at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	LENGTH OF COLLICULI	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5				
10				
15	0.695			57.0
20	0.775	0.75	10.8	63.1
25	0.845	0.75	9.8	69.3
30	0.920	0.75	8.9	75.4
35	0.995	0.75	8.2	81.5
40	1.070	0.75	7.6	87.8
45	1.145	0.75	7.0	93.9
50	1.220	0.75	6.6	100.0
55	1.295	0.75	6.2	106.2

(obtained by sectioning) show an absolute volume of 0.034 cc. at approximately the close of the first month, while his two largest fetuses (new-born) have a cord volume of about 3 cc.

The percentage increment of the spinal cord volume when determined for 5-cm. intervals of crown-heel body length (fig. 26, curve X) is 47 per cent for the 10-to-15-cm. interval. It rises to about 55 per cent for the 15-to-20-cm. interval, and then falls to about 25 per cent for the 50-to-55-cm. interval.

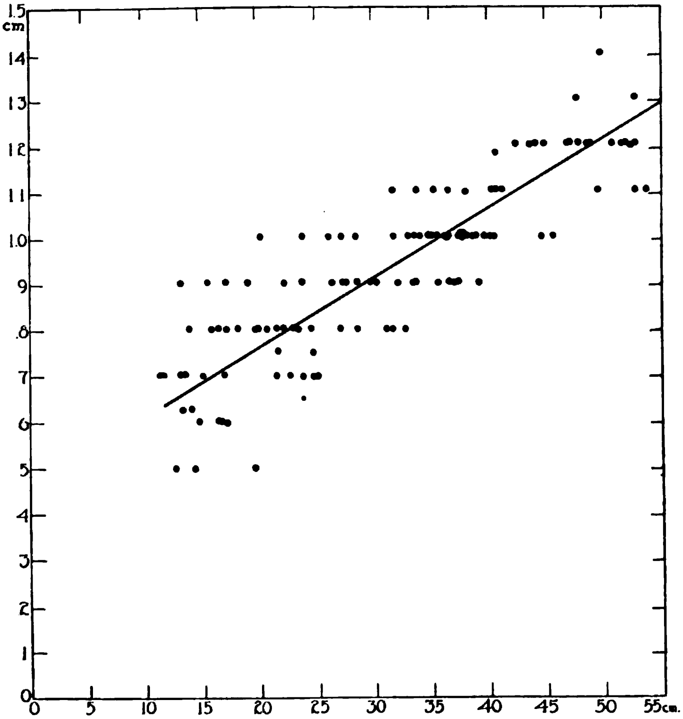

Fig. 19 Field graph and curve of the growth of the midbrain in fetal life as shown by the colliculi length. Abscissa: total body length in cm. Ordinate: colliculi length in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = 0.015X + 0.47$. (Data from tables 29 and 30.)

The percentage increment of the spinal cord volume when calculated for fetal months (fig. 28, curve I) shows a rate of growth of approximately 94 per cent in the fourth month and then descends steadily to 26 per cent in the last fetal month.

The relation of the spinal cord volume to the volume of the entire brain is shown in figure 22 and in table 40. At the middle of the second month the cord volume is equal to 4.4 per cent of the total brain volume. It then drops rapidly at first and afterward more slowly to about 0.85 per cent of the total brain volume at birth.

TABLE 31

Frontospinal length

Formula: Frontospinal length (cm.) = (2 crown-heel length (cm.))^{47} − 2.2

(145 cases)

CROWN-HEEL LENGTH		OBSERVED FRONTOSPINAL LENGTH			CALCULATED FRONTOSPINAL LENGTH	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5	4.0	1.0	0.7	0.9	0.5	−0.5	3
5 to 10	6.8	1.7	1.0	1.4	1.2	−0.2	9
10 to 15	12.1	2.9	1.9	2.1	2.3	+0.2	20
15 to 20	16.6	3.5	2.6	2.9	3.0	+0.1	14
20 to 25	22.6	4.5	3.0	3.8	3.8	0	20
25 to 30	27.0	4.6	3.4	4.1	4.3	+0.2	15
30 to 35	32.8	5.3	4.3	4.8	4.9	+0.1	17
35 to 40	37.1	6.5	4.0	5.3	5.4	+0.1	19
40 to 45	42.2	6.8	5.1	5.9	5.8	−0.1	12
45 to 50	48.2	6.9	5.9	6.3	6.4	+0.1	8
50 to 55	52.2	7.3	6.3	6.8	6.7	−0.1	8

TABLE 32

Calculated frontospinal length at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	CALCULATED FRONTOSPINAL LENGTH	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5	0.75			11.5
10	1.89	1.14	152.0	29.0
15	2.75	0.86	44.8	42.2
20	3.46	0.71	28.2	53.1
25	4.09	0.63	18.2	62.8
30	4.65	9.56	13.4	71.4
35	5.17	0.52	12.4	79.5
40	5.64	0.47	9.3	86.6
45	6.09	0.45	8.0	94.5
50	6.51	0.42	6.7	100.0
55	6.91	0.40	6.3	106.2

The absolute length of the spinal cord (fig. 23) ascends rather sharply from 2.2 cm. length at 5 cm. (C H) to 9.2 cm. at 25 cm. (C H). It then ascends more slowly to 14.2 cm. at birth (50 cm. C H). Its empirical formula is:

$$\text{Length of spinal cord (cm.)} = (10.0\ \text{C H body length (cm.)})^{.467} - 4.0$$

The curve of cord length, when plotted against time, is quite similar to that plotted against body length, but the rise is a more rapid one (fig. 32, curve IV).

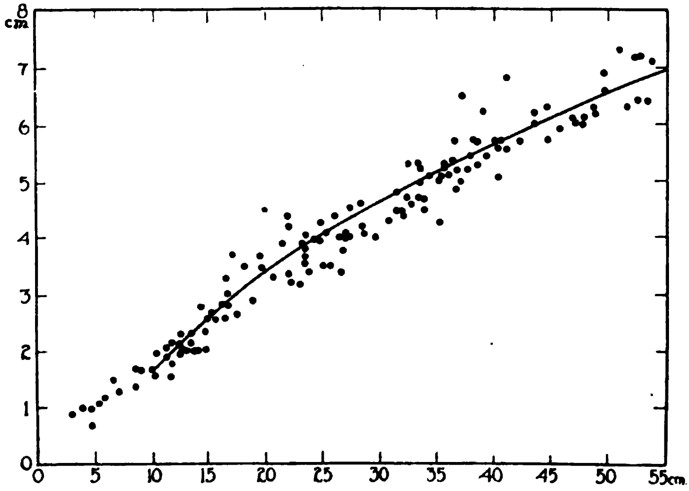

Fig. 20 Field graph and curve of the growth of the brain stem in fetal life as shown by the fronto-spinal length. Abscissa: total body length in cm. Ordinate: fronto-spinal length in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = (2.0X)^{.47} - 2.2$. (Data from tables 31 and 32.)

The percentage increment of the cord length as calculated for 5-cm. intervals of crown-heel length (fig. 25, curve VIII) is about 109 per cent for the 5-to-10-cm. interval, falls rapidly to 23 per cent for the 15-to-20-cm. interval, and then gradually to 6 per cent for the 50-to-55-cm. interval.

The percentage increment of the spinal-cord length when calculated for fetal months (fig. 27, curve V) shows a rate of growth of approximately 400 per cent in the third month, descending rapidly to 26 per cent in the sixth month, and then gradually to nearly 6 per cent in the last month of the fetal period.

DISCUSSION

The discussion of the results of this work will be limited to, 1) a comparison of the growth of the central nervous system as a whole with that of the various other viscera and parts of the body in the fetal period; 2) the analysis of the type of growth of the

TABLE 33

Volume of the spinal cord

Formula: Spinal cord volume (cc.) = .01 [(0.17 crown-heel length (cm.) $)^{2.57}$ + 11.]

(128 cases)

CROWN-HEEL LENGTH		OBSERVED VOLUME OF SPINAL CORD			CALCULATED VOLUME OF SPINAL CORD	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cc.*	*cc.*	*cc.*	*cc.*	*cc.*	
0 to 5							
5 to 10	7.2	0.05	0.05	0.05	0.13	0.08	3
10 to 15	12.5	0.3	0.1	0.2	0.2	0	18
15 to 20	16.5	0.5	0.1	0.3	0.3	0	14
20 to 25	22.6	0.7	0.3	0.5	0.4	−0.1	19
25 to 30	26.9	1.1	0.3	0.65	0.6	0	14
30 to 35	32.6	1.4	0.5	0.9	0.9	0	17
35 to 40	37.0	2.1	0.7	1.1	1.1	0	17
40 to 45	41.9	2.3	1.2	1.7	1.7	0	11
45 to 50	48.0	3.1	1.4	2.4	2.3	−0.1	7
50 to 55	52.2	3.8	1.8	2.5	2.8	+0.3	8

TABLE 34

Calculated spinal cord volume at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	SPINAL CORD VOLUME	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cc.*	*cc.*	*per cent*	*per cent*
5				
10	0.15			5.9
15	0.22	0.07	46.7	8.6
20	0.34	0.12	54.5	13.3
25	0.52	0.18	53.0	20.3
30	0.77	0.25	48.1	30.1
35	1.09	0.32	41.5	42.5
40	1.49	0.40	36.7	58.2
45	1.98	0.49	32.9	77.4
50	2.56	0.58	29.2	100.0
55	3.24	0.68	24.5	126.5

central nervous system into its component parts; 3) observations upon the relation of volumetric and lineal measurements of the nervous system, and, 4) a summary of the proportions which the various brain parts form of the encephalon in prenatal life. The consideration of the growth of the fetal brain and the spinal cord in relation to the postnatal changes of these structures is reserved for a later publication. It is hoped also that it will be possible

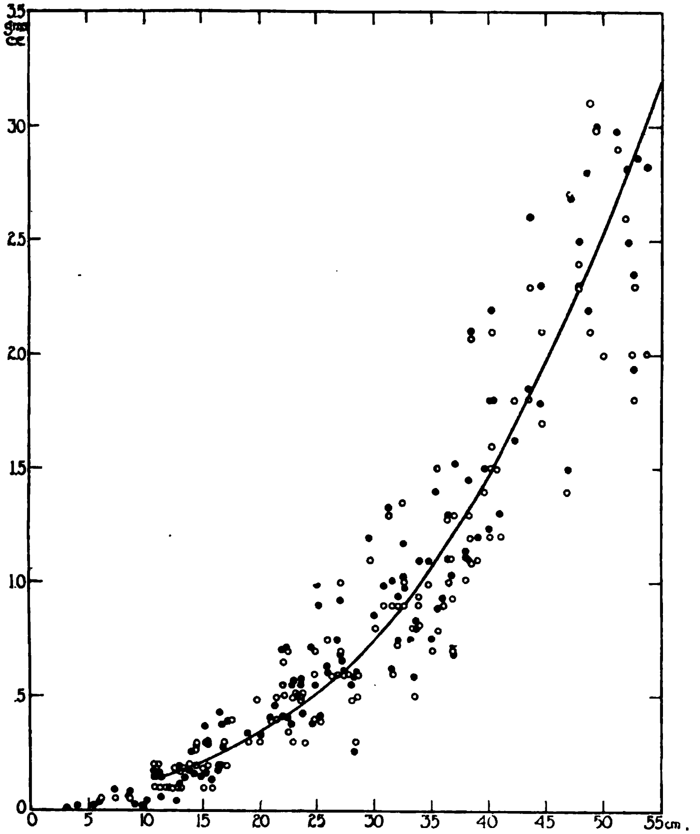

Fig. 21 Field graph and curve of the growth of the spinal cord in weight and volume during fetal life. Abscissa: total body length in cm. Ordinate: spinal cord weight and volume in grams (cc.). Individual cases indicated by solid dots (for weights) and by circles (for volume). Curve drawn to the formula: $Y = 0.01\,[(0.17X)^{2.57} + 11.0]$. (Data from tables 33, 34, 35.)

to present at a later time an outline of the prenatal growth of the various internal parts of the brain for which data are now being collected.

Growth of the central nervous system as a whole

The growth curve of the central nervous system (represented by the volume of the central nervous system, fig. 2) is analogous in both its character and its slope to the growth curves of nearly all the fetal viscera. The abscissa of this curve is the crown-heel length and represents a simple lineal type of growth. The value of the central nervous system is therefore a function of the crown-heel length which has been raised to approximately the third power. Obviously, this is a typical concave volumetric curve. It is similar in type to all of the visceral volumetric and ponderal curves of growth which have been worked out in this laboratory and of which a summary has been published elsewhere (Scammon, '21). It is also analogous to the curves of fetal body weight and of weights of body parts which have been expressed in functions of the crown-heel length of the fetus. In order to compare

TABLE 35

Spinal cord volume and weight

(data of Jackson, '09, and of Volpin, '02)

RANGE OF CROWN-HEEL LENGTH	SPINAL-CORD VOLUME (JACKSON, '09)			SPINAL-CORD WEIGHT (VOLPIN, '02)		
	Average crown-heel length	Average cord volume	Number of cases	Average crown-heel length	Average cord weight	Number of cases
cm.	*cm.*	*cc.*		*cm.*	*grams*	
0 to 5	1.77	0.02225	3			
5 to 10	7.7	0.115	3			
10 to 15	12.3	0.1671	3			
15 to 20	17.1	0.3447	5	16.0	0.75	1
20 to 25	22.4	0.664	4	20.0	1.5	1
25 to 30	27.4	0.908	5	28.0	2.0	1
30 to 35	32.7	1.53	2	32.7	3.0	3
35 to 40	38.5	1.8	1	38.5	3.75	2
40 to 45	44.2	3.3	1	41.8	4.5	3
45 to 50				45.7	6.6	3
50 to 55	51.9	3.04	2	51.0	9.5	3

the growth of the central nervous system to the growth of other parts of the body it has been considered as a unit. It is however a complex of four distinct subtypes of growth, all of which are dominated by the growth of the bulky cerebral hemispheres.[2]

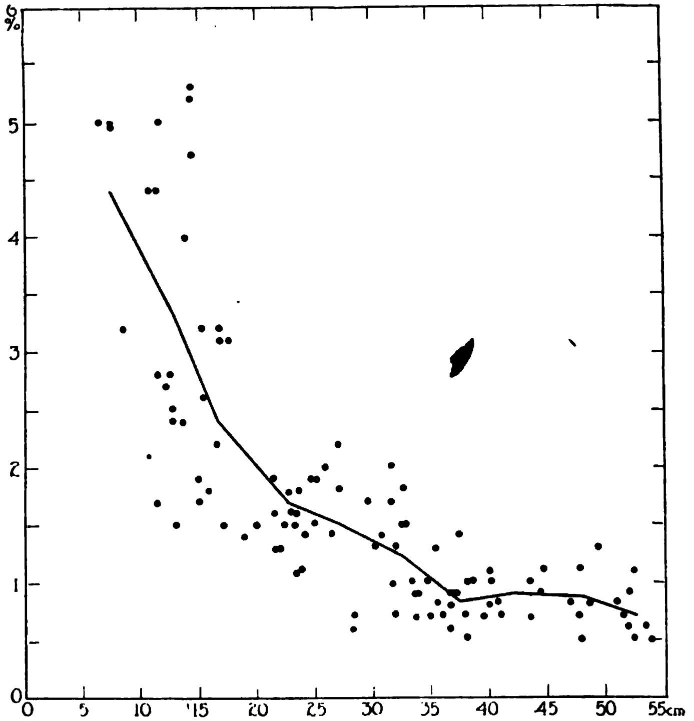

Fig. 22 Field graph and curve (connecting the average points of each 5-cm. crown-heel interval) of the per cent which the spinal cord volume forms of the encephalon volume. Abscissa: total body length in cm. Ordinate: spinal cord in per cent of the encephalon volume. Individual cases indicated by solid dots. (Data from table 40.)

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[2] In order to compare these four types of growth, ten methods were used: 1) the various absolute length curves (fig. 29) were calculated against crown-heel body length (cm.) and reduced to a percentage basis; 2) the absolute volume curves likewise (fig. 30) were taken to crown-heel length and reduced to a per cent basis; 3) the absolute length curves (fig. 33) were calculated for age in fetal months and reduced to a common per cent; 4) the absolute volume curves also (fig. 36) were taken to age in fetal months and reduced to a percentage basis; 5) percentage increments of linear curves (fig. 25) were calculated for 5-cm. C H intervals;

TABLE 36

Length of the spinal cord

Formula: Spinal cord length (cm.) = 10 crown-heel length $(\text{cm.})^{.447}$ − 4
(144 cases)

CROWN-HEEL LENGTH		OBSERVED SPINAL CORD LENGTH			CALCULATED SPINAL CORD LENGTH	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maximum	Minimum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5	3.9	2.5	1.4	1.9	1.4	−0.5	4
5 to 10	7.7	4.0	2.3	3.0	3.6	+0.6	9
10 to 15	12.1	6.2	4.0	4.7	5.4	+0.7	20
15 to 20	16.7	9.7	5.3	7.0	6.9	−0.1	14
20 to 25	22.7	10.7	7.0	8.7	8.6	−0.1	20
25 to 30	26.9	10.7	8.5	9.75	9.6	−0.1	14
30 to 35	32.6	13.3	9.0	10.6	10.9	+0.3	18
35 to 40	37.1	16.5	9.5	12.2	11.8	−0.4	17
40 to 45	42.2	14.0	11.0	12.4	12.8	+0.4	12
45 to 50	48.2	14.8	12.7	13.5	13.9	+0.4	8
50 to 55	52.2	15.8	13.2	14.5	14.6	+0.1	8

TABLE 37

Calculated spinal cord length at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	SPINAL CORD LENGTH	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5	2.2			15.5
10	4.6	2.4	109.0	32.4
15	6.4	1.8	39.2	45.0
20	7.9	1.5	23.4	55.6
25	9.2	1.3	16.4	64.8
30	10.4	1.2	13.0	73.3
35	11.4	1.0	9.6	80.3
40	12.4	1.0	8.2	87.3
45	13.3	0.9	7.5	94.0
50	14.2	0.9	6.5	100.0
55	15.0	0.8	5.9	105.6

6) percentage increments of volume curves (fig. 26) were determined for 5-cm. intervals; 7) percentage increments of linear curves (fig. 27) were calculated for age in fetal months; 8) percentage increments of linear curves (fig. 28) were determined for age in fetal months; 9) the various linear formulae of the respective absolute curves (table 43), and, 10) the volumetric formulae of the absolute volume curves (table 43) were compared.

The first type, cerebral growth, is characterized by a constant growth in linear measurements from the second fetal month until birth, and shows a steady and relatively slow increase in volume

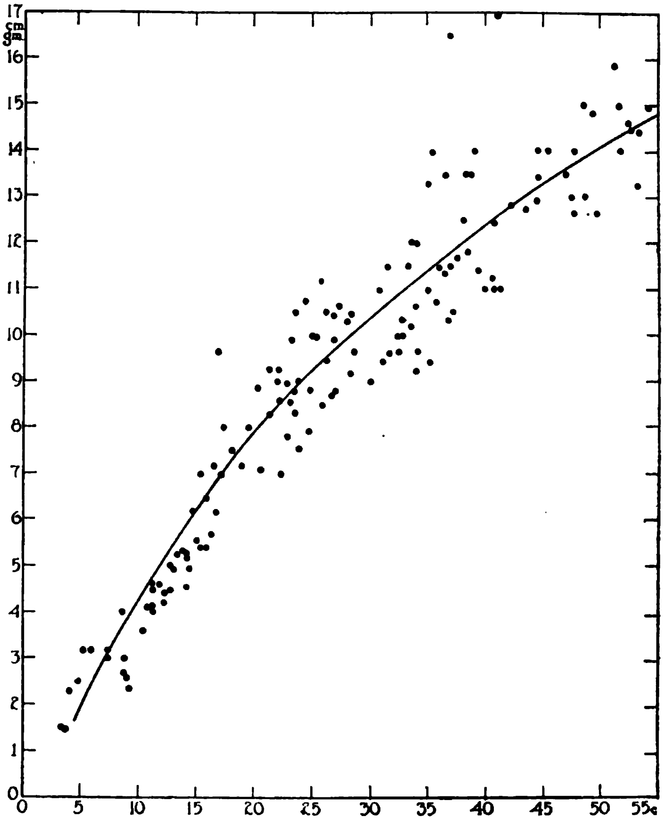


Fig. 23 Field graph and curve of the growth of the spinal cord in fetal life as shown by the spinal cord length. Abscissa: total body length in cm. Ordinate: spinal cord length in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = (10.0X)^{.467} - 4.0$. (Data from tables 36 and 37.)

before the sixth fetal month and a constant but more rapid increase from that time until birth. Brain stem and cord growth, on the other hand, advances much faster previous to the seventh fetal month than it does in the last four months of fetal life. Cerebellum growth, on the contrary, proceeds slowly until the seventh fetal month and from that time until birth it exceeds all other growth activity in the central nervous system. The last type, compound growth, represents merely the combined effect of two or more of the above types predominated by the mass of the cerebral hemispheres. These varieties of growth will now be considered in more detail.

TABLE 38

Combined brain-cord length

Formula: Brain-cord length (cm.) = $(10 \text{ crown-heel length (cm.)})^{.514} - 4$

(137 cases)

CROWN-HEEL LENGTH		OBSERVED BRAIN-CORD LENGTH			CALCULATED BRAIN-CORD LENGTH	DIFFERENCE BETWEEN OBSERVED AND CALCULATED MEANS	NUMBER OF CASES
Range	Mean	Maxi-mum	Mini-mum	Mean			
cm.	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	*cm.*	
0 to 5	4.0	4.9	3.1	3.0	2.7	−0.3	3
5 to 10	7.1	5.7	4.0	4.4	4.9	+0.5	7
10 to 15	12.1	8.5	5.0	6.9	7.8	+0.9	20
15 to 20	16.6	12.7	7.9	9.8	9.8	0	14
20 to 25	22.6	14.7	10.2	12.4	12.2	−0.2	19
25 to 30	26.9	15.1	12.1	13.8	13.8	0	13
30 to 35	32.8	18.4	14.1	15.4	15.6	−0.2	16
35 to 40	37.1	20.2	13.5	17.4	16.9	−0.5	17
40 to 45	42.2	19.7	16.1	18.1	18.4	−0.3	11
45 to 50	48.2	21.7	18.8	19.8	19.9	+0.1	9
50 to 55	52.2	23.1	20.4	21.3	20.9	−0.4	8

TABLE 39

Calculated combined brain-cord length at 5-cm. intervals of crown-heel length

CROWN-HEEL LENGTH	BRAIN-CORD LENGTH	INCREMENT IN EACH 5-CM. INTERVAL		RATIO TO NEW-BORN
cm.	*cm.*	*cm.*	*per cent*	*per cent*
5	3.5			17.2
10	6.6	3.1	88.5	32.3
15	9.2	2.6	39.4	45.1
20	11.2	2.0	21.7	54.9
25	13.1	1.9	17.0	64.2
30	14.8	1.7	13.0	72.5
35	16.3	1.5	10.1	79.9
40	17.8	1.5	9.2	87.2
45	19.1	1.3	7.3	93.6
50	20.4	1.3	6.4	100.0
55	21.6	1.2	5.9	106.0

Cerebral growth. The growth of the cerebrum is characterized by a steady absolute increment in all of its linear measurements from the second fetal month until birth. This can be observed by the inspection of the curves of the fronto-occipital length and the temporal diameter (fig. 29, curves I and II, respectively).

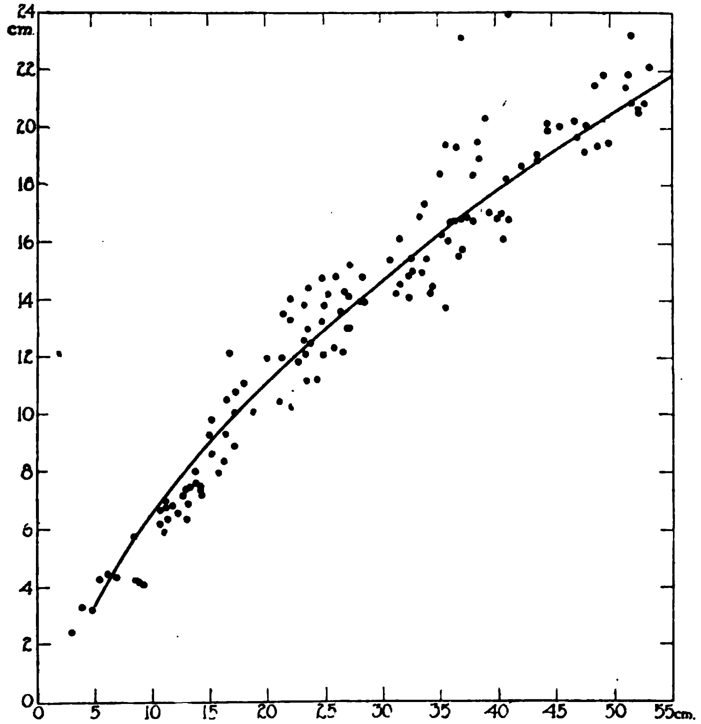


Fig. 24 Field graph and curve of the growth of the spinal cord and brain stem in fetal life as shown by the brain-cord length. Abscissa: total body length in cm. Ordinate: brain-cord length in cm. Individual cases indicated by solid dots. Curve drawn to the formula: $Y = (10.0X)^{.514} - 4.0$. (Data from tables 38 and 39.)

These curves are both straight lines and lie intermediate to the vermis cerebelli absolute curves below and to the curve of the spinal cord above. When calculated against time in fetal months (fig. 33, curves I and II), the fronto-occipital length and the

(*Text continued on page 479*)

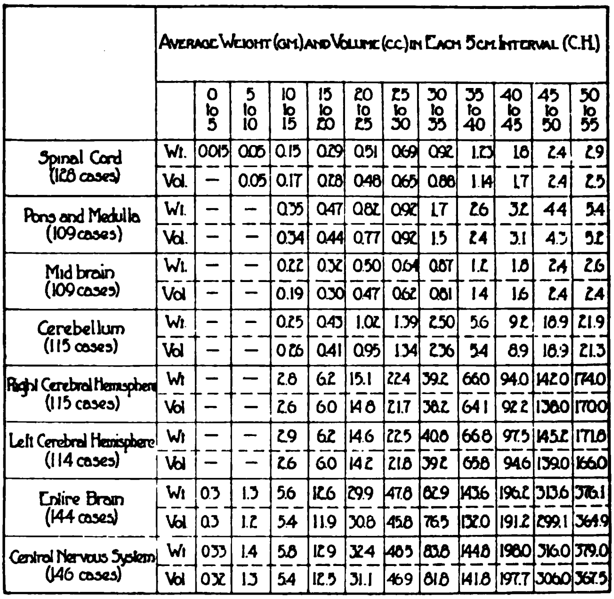
TABLE 40

Ratios of the volumes of the various parts of the central nervous system to the entire brain volume

CROWN-HEEL LENGTH RANGE	RATIO OF:				
	Spinal cord	Pons and medulla	Midbrain	Cerebellum	Cerebral hemispheres
cm.					
5 to 10	4.70				
10 to 15	3.30	5.5	2.90	3.0	87.7
15 to 20	2.40	3.6	2.40	3.0	90.9
20 to 25	1.70	2.7	1.60	3.1	93.1
25 to 30	1.50	2.2	1.40	3.0	94.0
30 to 35	1.20	1.9	0.96	2.8	94.2
35 to 40	0.81	1.7	0.90	3.8	94.1
40 to 45	0.90	1.6	0.87	4.4	93.2
45 to 50	0.84	1.5	0.70	6.2	92.0
50 to 55	0.70	1.4	0.67	5.8	91.8

TABLE 41

COMPARISON OF THE WEIGHTS AND VOLUMES OF THE SPINAL CORD, THE ENTIRE BRAIN AND THE VARIOUS PARTS OF THE BRAIN IN THE FETAL PERIOD



		AVERAGE WEIGHT (GM.) AND VOLUME (CC.) IN EACH 5 CM. INTERVAL (C.H.)										
		0 to 5	5 to 10	10 to 15	15 to 20	20 to 25	25 to 30	30 to 35	35 to 40	40 to 45	45 to 50	50 to 55
Spinal Cord (128 cases)	Wt.	0.015	0.05	0.15	0.29	0.51	0.69	0.92	1.23	1.8	2.4	2.9
	Vol.	—	0.05	0.17	0.28	0.48	0.65	0.88	1.14	1.7	2.4	2.5
Pons and Medulla (109 cases)	Wt.	—	—	0.35	0.47	0.82	0.92	1.7	2.6	3.2	4.4	5.4
	Vol.	—	—	0.34	0.44	0.77	0.92	1.5	2.4	3.1	4.3	5.2
Mid brain (109 cases)	Wt.	—	—	0.22	0.32	0.50	0.64	0.87	1.2	1.8	2.4	2.6
	Vol	—	—	0.19	0.30	0.47	0.62	0.81	1.4	1.6	2.4	2.4
Cerebellum (115 cases)	Wt.	—	—	0.25	0.43	1.02	1.39	2.50	5.6	9.2	18.9	21.9
	Vol	—	—	0.26	0.41	0.95	1.34	2.36	5.4	8.9	18.9	21.3
Right Cerebral Hemisphere (115 cases)	Wt	—	—	2.8	6.2	15.1	22.4	39.2	66.0	94.0	142.0	174.0
	Vol	—	—	2.6	6.0	14.8	21.7	38.2	64.1	92.2	138.0	170.0
Left Cerebral Hemisphere (114 cases)	Wt	—	—	2.9	6.2	14.6	22.5	40.8	66.8	97.5	145.2	171.8
	Vol	—	—	2.6	6.0	14.2	21.8	39.2	65.8	94.6	139.0	166.0
Entire Brain (144 cases)	Wt	0.3	1.3	5.6	12.6	29.9	47.8	82.9	143.6	196.2	313.6	376.1
	Vol	0.3	1.2	5.4	11.9	30.8	45.8	76.5	132.0	191.2	299.1	364.9
Central Nervous System (146 cases)	Wt	0.33	1.4	5.8	12.9	32.4	48.5	83.8	144.8	198.0	316.0	379.0
	Vol	0.32	1.3	5.4	12.5	31.1	46.9	81.8	141.8	197.7	306.0	367.5

TABLE 42
CALCULATED ABSOLUTE AND PERCENTAGE INCREMENTS OF THE SEVERAL PARTS OF THE BRAIN AND OF THE SPINAL CORD IN EACH MONTH OF THE FETAL PERIOD

Age According to Mall's Tables (Fetal Months)	Cerebrum						Cerebellum						Pons and Medulla				Midbrain		Spinal Cord			
	Both Hemispheres Volume		Fronto occipital Length		Temporal Diameter		Cerebellum Volume		Vermis Cerebelli Length		Vermis Cerebelli Height		Pons and Medulla Volume		Pons Length		Mid brain Volume		Spinal Cord Volume		Spinal Cord Length	
	c.c	%	cm.	%	cm.	%	c.c.	%	cm.	%	cm.	%	c.c	%	cm.	%	c.c.	%	c.c	%	cm.	%
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	ca. 0.04	—	0.77	—	0.71	—	0.20	—	0.22	—	0.05	—	0.20	—	0.24	—	0.12	—	0.04	—	0.90	—
3	1.68	ca 4250.	1.96	153.0	1.65	131	0.27	35.	0.40	81.8	0.23	360.	0.26	30.0	0.42	74.8	0.16	33.3	0.15	36.4	4.51	401.
4	11.67	596.	3.40	73.0	2.78	68.5	0.34	30.	0.74	85.0	0.52	126.	0.51	96.2	0.63	51.6	0.29	81.3	0.29	93.3	7.30	62.
5	33.27	185	4.62	36.0	3.75	34.7	0.89	161.5	1.09	47.3	0.82	57.6	0.93	82.4	0.82	29.1	0.51	75.8	0.52	79.3	9.16	25.8
6	69.53	109	5.76	24.6	4.65	23.9	2.25	153.0	1.45	33.0	1.13	37.8	1.56	67.8	0.99	20.9	0.83	62.8	0.86	65.4	10.66	16.3
7	117.2	68.5	6.74	17.0	5.42	16.7	4.99	121.9	1.78	22.8	1.41	24.7	2.31	48.0	1.14	14.9	1.20	44.6	1.25	45.4	11.84	10.9
8	180.6	54.2	7.69	14.0	6.16	13.8	9.53	91.0	2.13	19.7	1.70	20.6	3.23	39.8	1.28	12.5	1.65	37.5	1.72	37.6	12.88	8.8
9	249.2	37.8	8.47	10.2	6.79	10.1	15.84	66.3	2.43	14.1	1.95	14.7	4.17	29.1	1.34	9.3	2.10	27.3	2.20	27.9	13.70	6.4
10	300.6	35.	9.00	9.5	7.20	9.2	20.89	54.2	2.64	12.4	2.13	13.2	4.88	27.5	1.47	7.3	2.44	25.	2.56	26.	14.21	5.7

TABLE 43
EMPIRICAL FORMULAE REPRESENTING CURVES OF LINEAR AND VOLUMETRIC GROWTH OF THE CENTRAL NERVOUS SYSTEM IN THE FETAL PERIOD

Measurement	Specific Formulae (Exponential)	Type of Formula	Specific Formulae (Logarithmic)	Type of Formula
Fronto-occipital Length	$Y=0.175X+0.25$	$Y=aX+b$	$Y=0.175X+0.25$	$Y=aX+b$
Temporal-temporal Diameter	$Y=0.138X+0.3$		$Y=0.138X+0.3$	
Pons Length	$Y=0.0263X+0.16$		$Y=0.0263X+0.16$	
Colliculi Length	$Y=0.015X+0.47$		$Y=0.015X+0.47$	
Spinal Cord Length	$Y=(10.0X)^{.467}-4.0$	$Y=(aX)^b-c$	$Y=0.07X+10\log X-6.5$	$Y=aX+b\log X-c$
Brain Cord Length	$Y=(10.0X)^{.514}-4.0$		$Y=0.17X+11\log X-6.7$	
Fronto-spinal Length	$Y=(2.0X)^{.47}-2.2$		$Y=0.051X+4\log X-2.85$	
Vermis Cerebelli Length	$Y=0.01(X^{1.41}+15.0)$	$Y=0.01(X^a+b)$	$Y=0.01(0.073X+2.85)^3$	$Y=0.01(aX+b)^3$
Vermis Cerebelli Height	$Y=0.01(X^{1.37})$		$Y=0.01(.07X+2.45)^3$	
Spinal Cord Volume	$Y=0.01[(0.17X)^{2.57}+11.0]$	$Y=0.01[(aX)^b+c]$	$Y=1.4(0.02X+0.31)^3-0.013X+0.1$	$Y=a(bX+c)^3\pm dX+e$
Pons and Medulla Volume	$Y=0.01[(0.2X)^{2.67}+20.0]$		$Y=0.94(0.03X+0.2)^3+0.1$	
Mid Brain Volume	$Y=0.01[(0.168X)^{2.56}+12.0]$		$Y=1.5(0.02X+0.31)^3-0.027X+0.38$	
Cerebellum Volume	$Y=0.01[(0.095X)^{4.9}+20.0]$		$Y=0.01(0.026X+1.03)^9$	$Y=0.01(aX+b)^9$
Right Hemisphere Volume	$Y=(0.1X)^{3.13}$	$Y=(aX)^b$	$Y=(0.1085X-0.09)^3$	$Y=a(bX-c)^3$
Left Hemisphere Volume	$Y=(0.105X)^{3.04}$		$Y=(0.108X-0.05)^3$	
Both Hemispheres Volume	$Y=(0.12X)^{3.19}$			
Encephalon Volume	$Y=(0.125X)^{3.16}+1.5$	$Y=(aX)^b+c$	$Y=1.1(0.137X-0.07)^3-0.4X+5.0$	$Y=a(bX\pm c)^3-dX+e$
Encephalon Weight	$Y=(0.13X)^{3.19}+1.0$		$Y=1.15(0.14X+0.2)^3-X+10.0$	
Central Nervous System Volume	$Y=(0.114X)^{3.34}+2.0$		$Y=1.17(0.137X-0.03)^3-1.12X+16.0$	

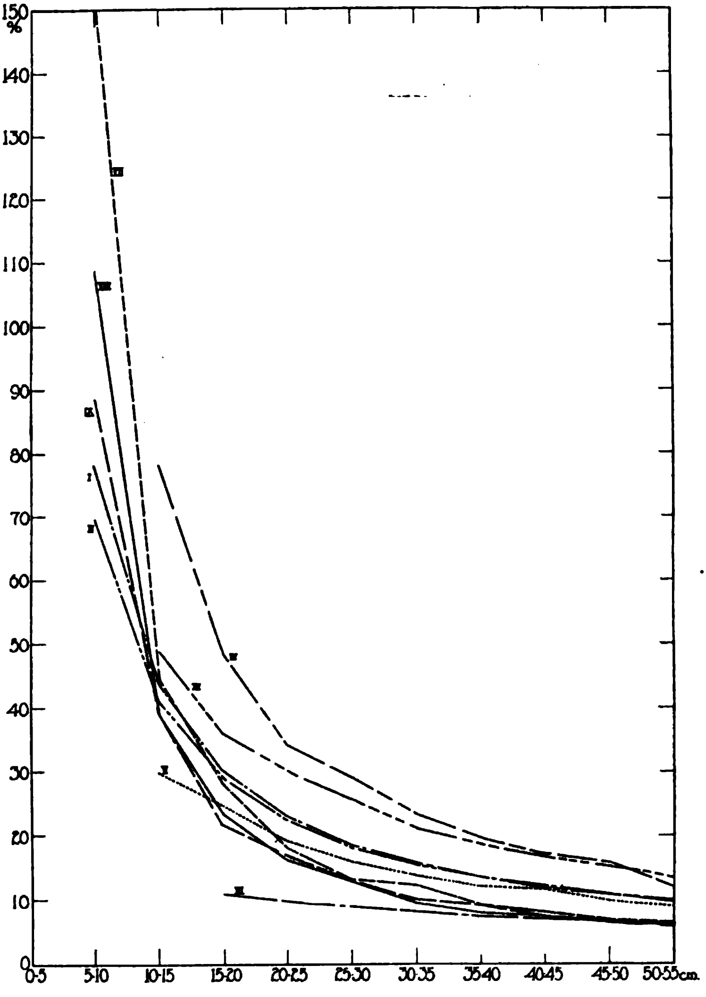


Fig. 25 A series of curves illustrating the percentage increments of the various linear dimensions of the brain, brain parts, and spinal cord. Abscissa: total body length in cm. Ordinates: percentage increments calculated from the formulae of the respective absolute curves. (Data from tables 14, 16, 20, 22, 26, 30, 32, 37, and 39.) I, percentage increment of fronto-occipital diameter. II, percentage increment of temporal diameter. III, percentage increment of vermis cerebelli length. IV, percentage increment of vermis cerebelli height. V, percentage increment of pons length. VI, percentage increment of colliculi length. VII, percentage increment of frontospinal length. VIII, percentage increment of spinal cord length. IX, percentage increment of brain-cord length.

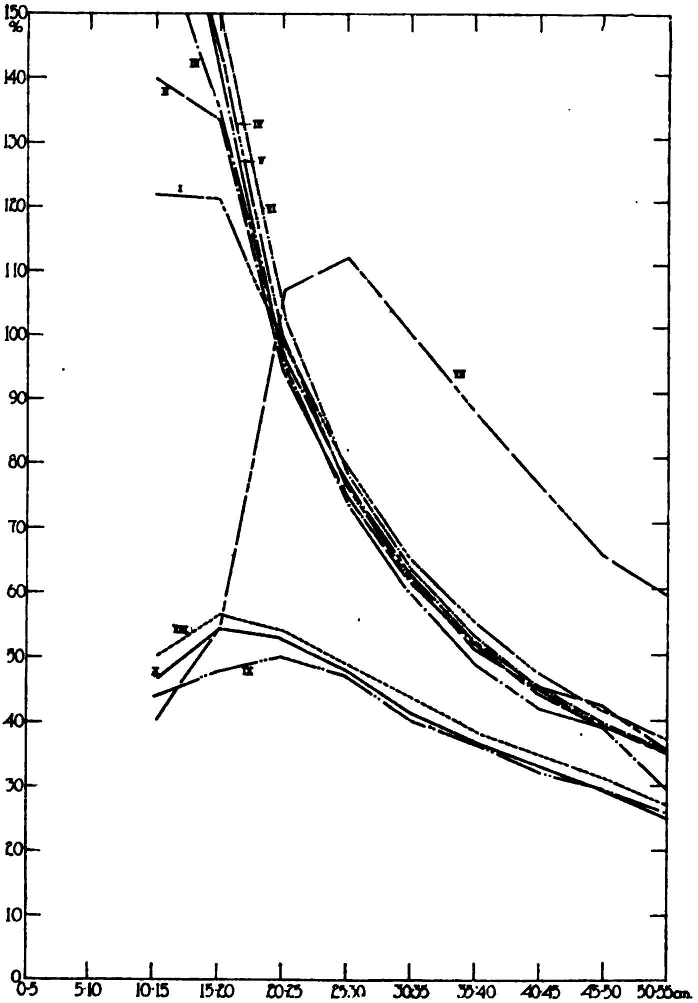


Fig. 26 A series of curves illustrating the percentage increments of the various volumetric determinations of the brain, brain parts, and spinal cord. Abscissa: total body length in cm. Ordinates: percentage increments calculated from the formulae of the respective absolute growth curves. (Data from tables 2, 4, 5, 8, 10, 12, 18, 24, 28, and 34.) I, percentage increment of central nervous system volume. II, percentage increment of encephalon volume. III, percentage increment of entire brain weight by literature. IV, percentage increment of right hemisphere volume. V, percentage increment of left hemisphere volume. VI, percentage increment of both hemisphere volume. VII, percentage increment of cerebellum volume. VIII, percentage increment of pons and medulla volume. IX, percentage increment of midbrain volume. X, percentage increment of spinal cord volume.

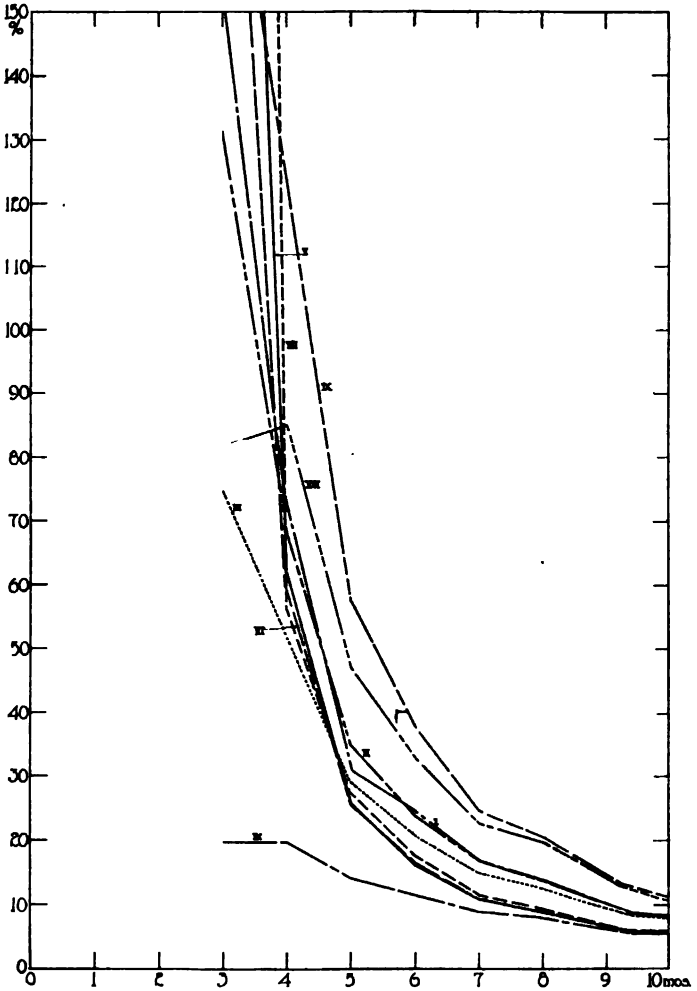


Fig. 27 A series of curves illustrating the percentage increments of the various linear dimensions of the brain, brain parts, and spinal cord when interpreted in time in fetal months (as determined by Mall's convention). Abscissa: total time of fetal life in months. Ordinate: percentage increments calculated from the formulae of corresponding absolute curves and transposed into time. (Data from table 41.) I, percentage increment of fronto-occipital diameter. II, percentage increment of temporal diameter. III, percentage increment of pons length. IV, percentage increment of colliculi length. V, percentage increment of spinal cord length. VI, percentage increment of brain-cord length. VII, percentage increment of frontospinal length. VIII, percentage increment of vermis cerebelli length. IX, percentage increment of vermis cerebelli height.

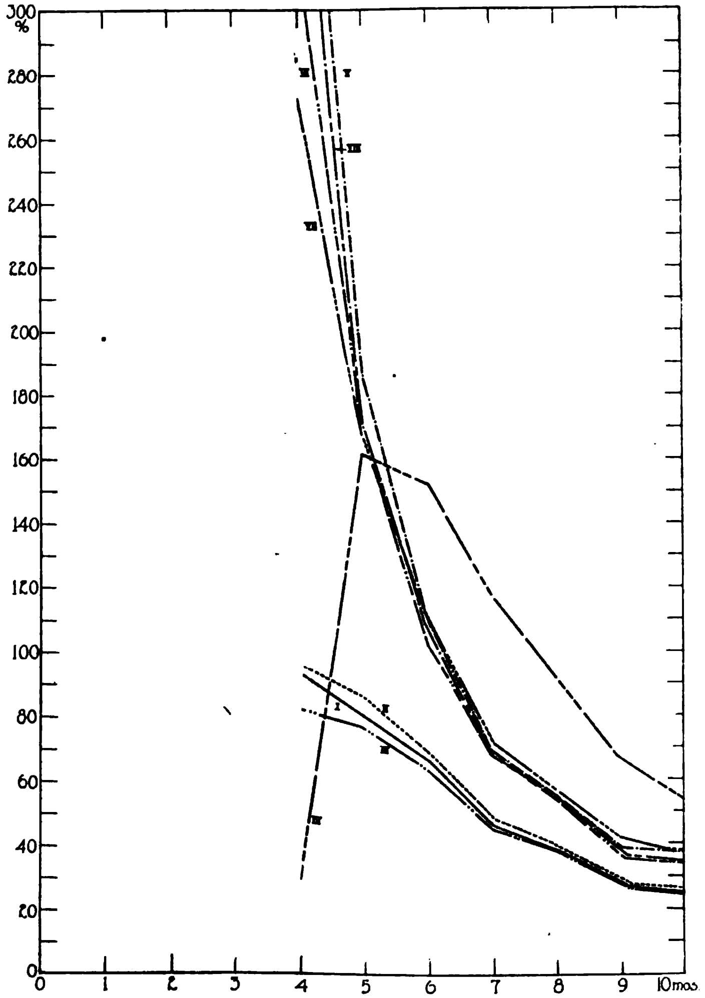


Fig. 28 A series of curves illustrating the percentage increment of the various volumetric determinations of the brain, brain parts, and spinal cord. Abscissa: total time in fetal months as determined by Mall's convention. Ordinates: percentage increments calculated from the formulae of respective absolute growth curves. (Data from tables 2, 4, 5, 8, 10, 12, 18, 24, 28, and 34.) I, percentage increment of spinal cord volume. II, percentage increment of pons and medulla volume. III, percentage increment of midbrain volume. IV, percentage increment of cerebellum volume. V, percentage increment of both hemisphere volume. VI, percentage increment of the encephalon volume. VII, percentage increment of the volume of the central nervous sytem. VIII, percentage increment of the encephalon weight (cases collected from the literature).

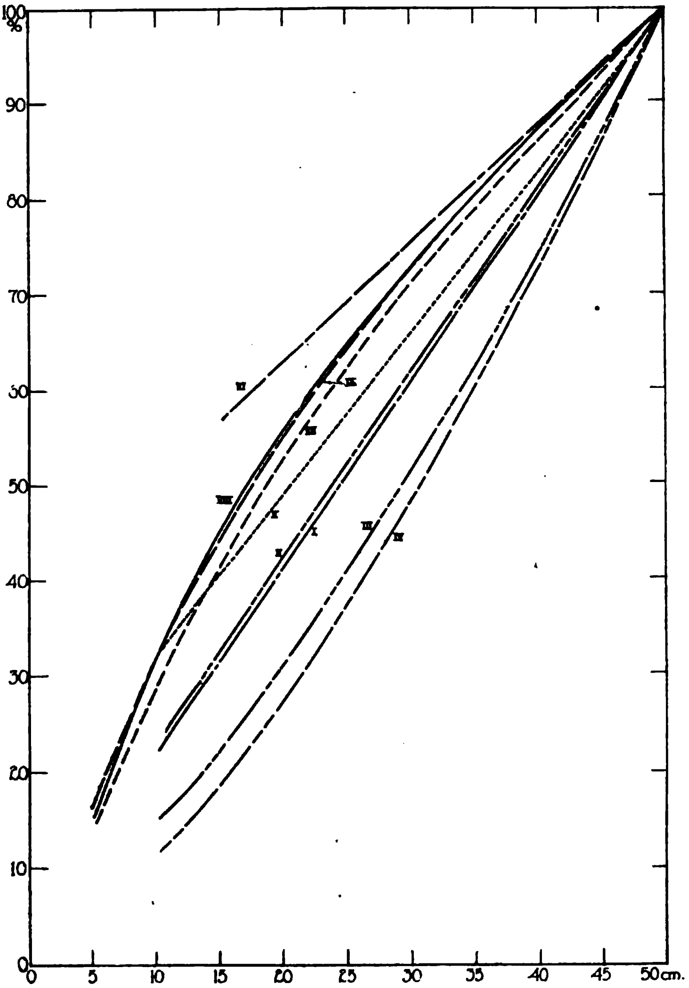


Fig. 29 A series of curves illustrating the growth (in linear dimensions) of the brain, brain parts, and spinal cord in per cent of the respective new-born linear measurements. Abscissa: total body length in cm. Ordinates: linear dimensions calculated in per cents of the respective new-born measurements. Data from the formulae in table 43. I, frontal-occipital diameter. II, temporal diameter. III, vermis cerebelli length. IV, vermis cerebelli height. V, pons length. VI, colliculi length. VII, frontospinal length. VIII, spinal cord length. IX, brain-cord length.

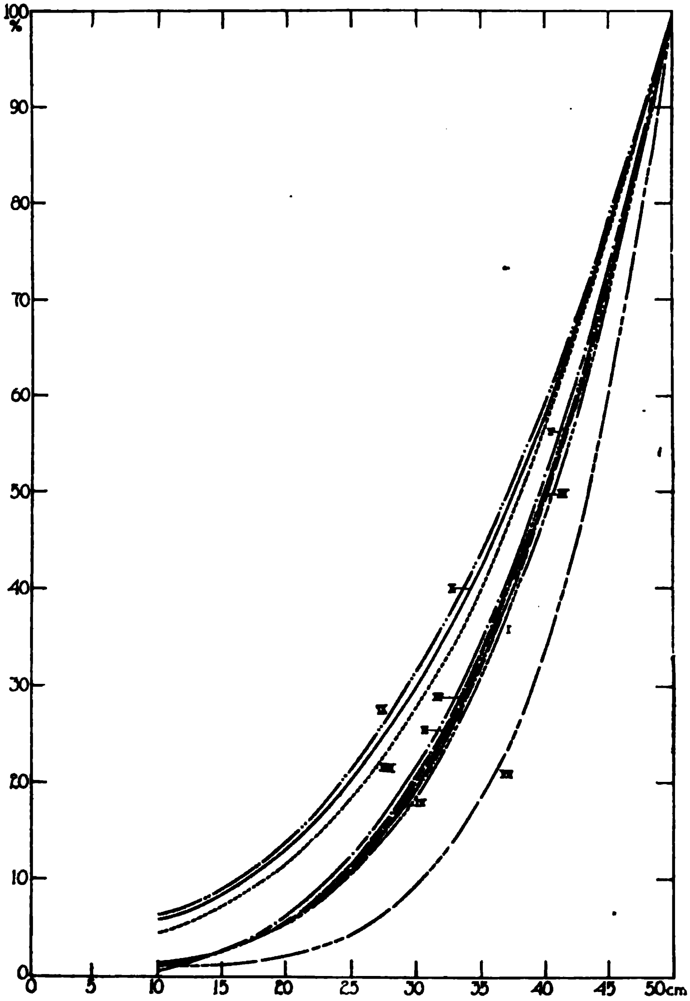


Fig. 30 A series of curves illustrating the growth in the volumes of the brain, brain parts, and spinal cord in per cent of the respective new-born volumetric determinations. Abscissa: total body length in cm. Ordinate: volumes calculated in per cents of the respective new-born volumetric determinations. (Data from the formulae in table 43.) I, volume of the central nervous system. II, encephalon volume. III, encephalon weight by cases from the literature. IV, right hemisphere volume. V, left hemisphere volume. VI, both hemisphere volumes. VII, cerebellum volume. VIII, pons and medulla volume. IX, midbrain volume. X, spinal-cord volume.

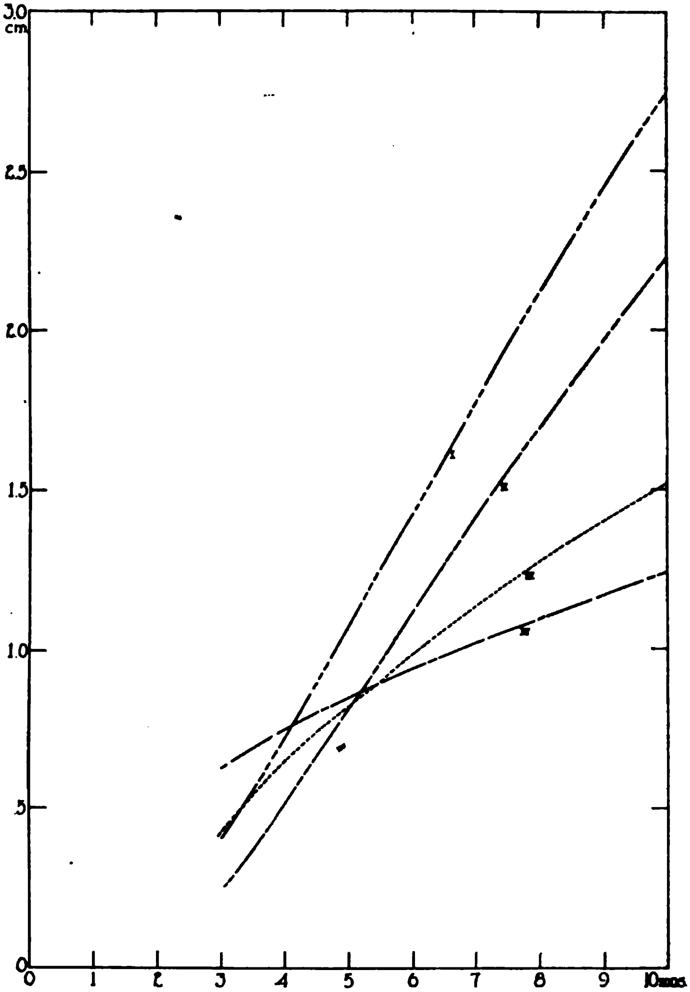


Fig. 31 A series of curves illustrating the growth of the pons, colliculi, and vermis cerebelli by linear measurements. Abscissa: fetal months (crown-heel reduced to time by Mall's convention). Ordinates: lengths of pons, colliculi, and vermis cerebelli in cm. (Data from formulae in table 43.) I, vermis cerebelli length. II, vermis cerebelli height. III, pons length. IV, colliculi length.

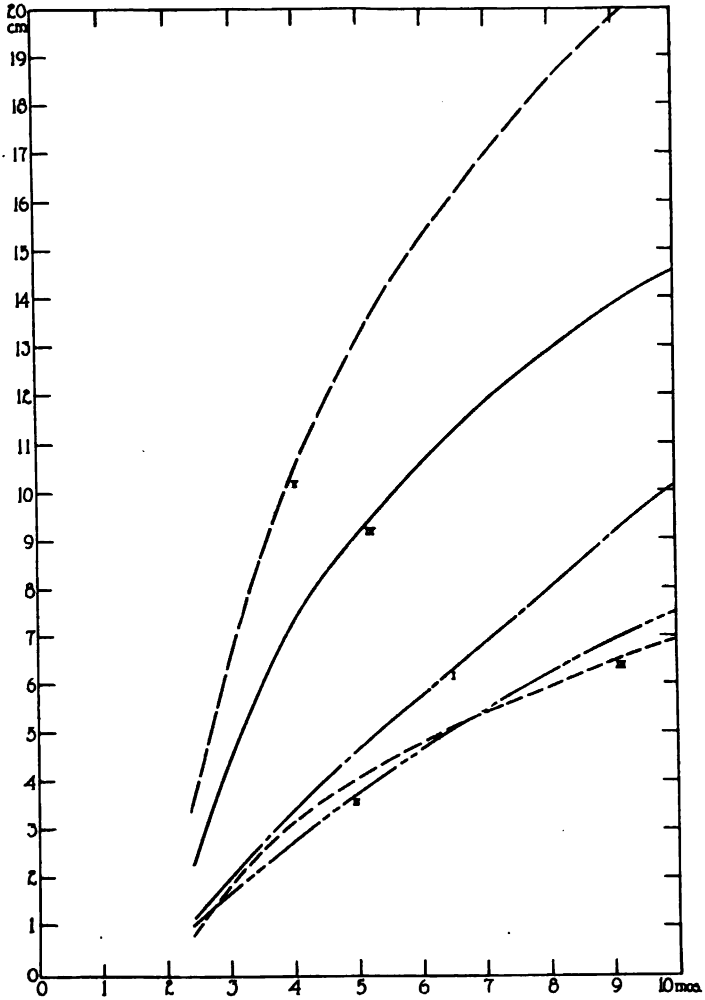


Fig. 32 A series of curves illustrating by linear measurements the growth of the cerebrum, brain stem, and spinal cord. Abscissa: fetal months (crown-heel reduced to time by Mall's convention). Ordinates: lengths of the cerebrum, brain stem, and spinal cord in cm. (Data from formulae in table 43.) I, fronto-occipital diameter. II, temporal diameter. III, frontospinal length. IV, spinal cord length. V, brain-cord length.

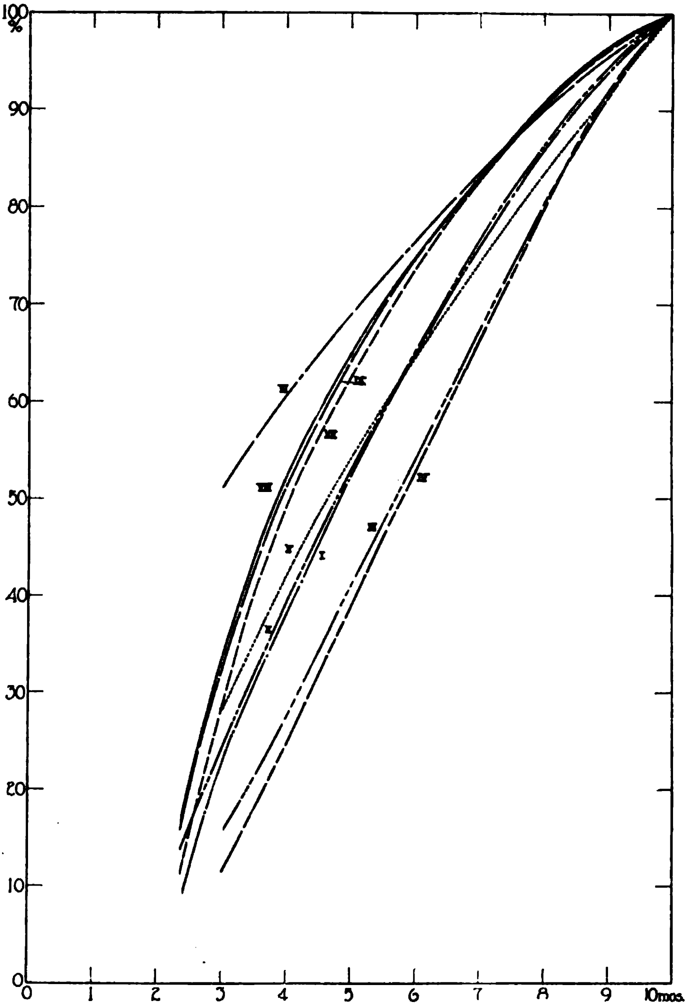


Fig. 33 A series of curves illustrating the growth (in linear dimensions) of the brain, brain parts, and spinal cord calculated in per cents of the respective new-born linear measurements. Abscissa: fetal months (crown-heel length reduced to time by Mall's convention). Ordinates: linear dimensions calculated in per cents of the respective new-born measurements. (Data from the formulae in table 43.) I, fronto-occipital diameter. II, temporal diameter. III, vermis cerebelli length. IV, vermis cerebelli height. V, pon length. VI, colliculi length. VII, frontospinal length. VIII, spinal-cord length. IX, brain-cord length.

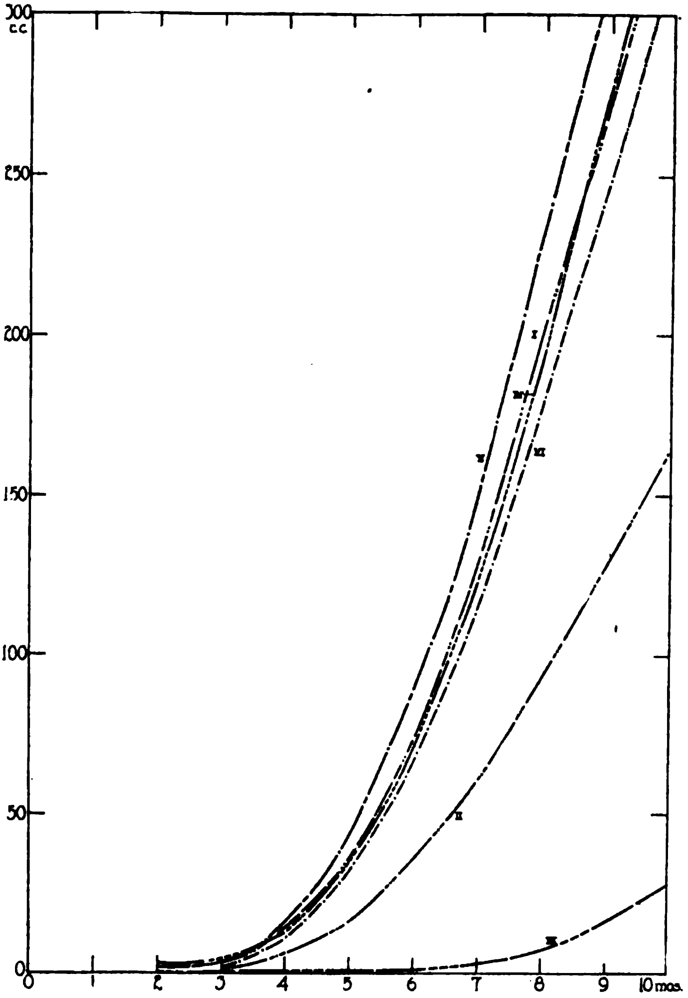


Fig. 34 A series of curves illustrating the growth of the cerebrum and cerebellum as shown by volumetric determinations. Abscissa: fetal months (crown-heel length reduced to time by Mall's convention). Ordinates: volumes of the encephalon, right hemisphere, and cerebellum. (Data from formulae in table 43.) I, encephalon volume. II, right hemisphere volume. III, cerebellum volume. IV, central nervous sytem volume. V, encephalon weight (data collected from the literature). VI, both hemisphere volume.

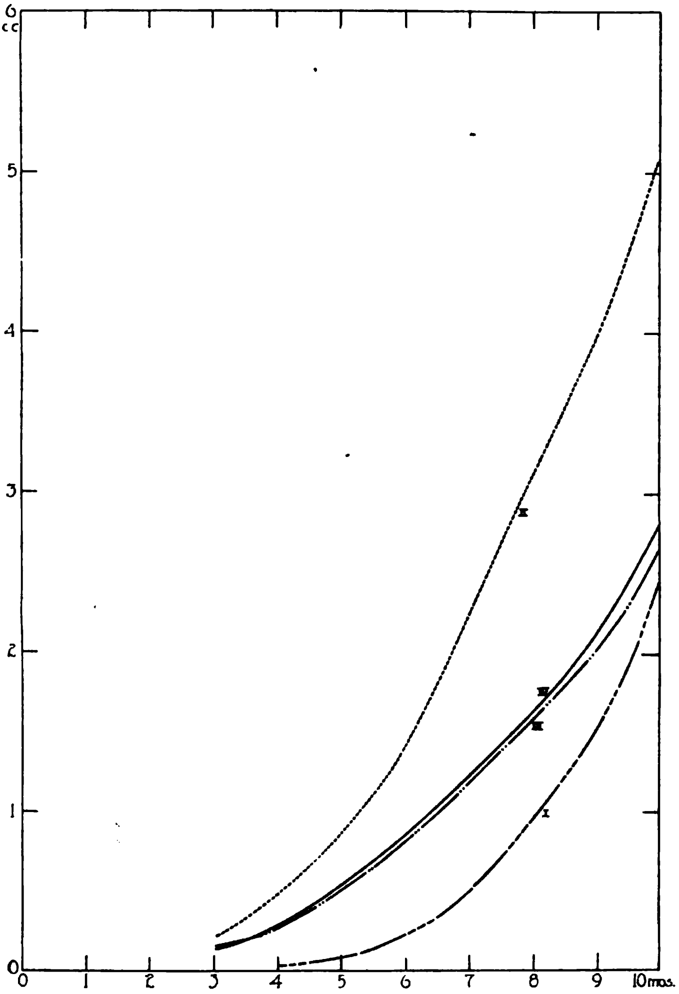


Fig. 35 A series of curves illustrating the growth of the cerebellum, pons and medulla, midbrain, and spinal cord. Abscissa: fetal months (crown-heel reduced to time by Mall's convention). Ordinates: volumes of the cerebellum, pons and medulla, midbrain, and spinal cord. (Data from the formulae in table 43.) I, cerebellum volume. II, pons and medulla volume, III, midbrain volume. IV, spinal cord volume.

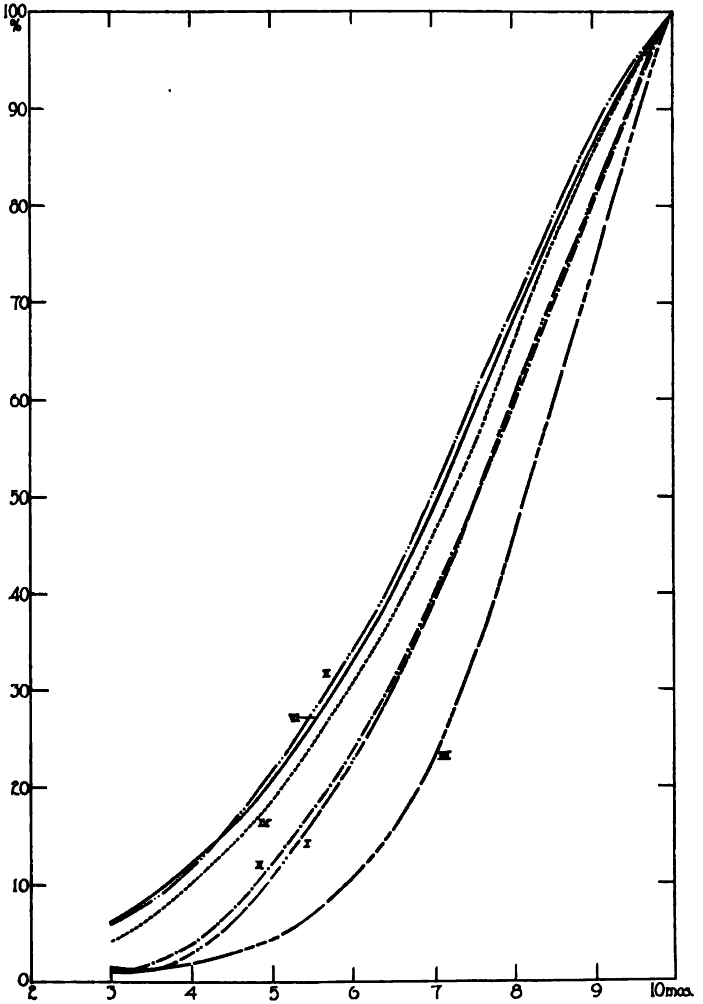


Fig. 36 A series of curves illustrating growth of the brain, brain parts, and spinal cord in per cent of the respective new-born volumetric determinations. Abscissa: fetal months (crown-heel reduced to time by Mall's convention). Ordinates: per cents of volumes as compared with the respective new-born volumetric determinations. (Data from the formulae in table 43.) I, encephalon volume. II, cerebral hemispheres volume. III, cerebellum volume. IV, pons and medulla volume. V, midbrain volume. VI, spinal cord volume.

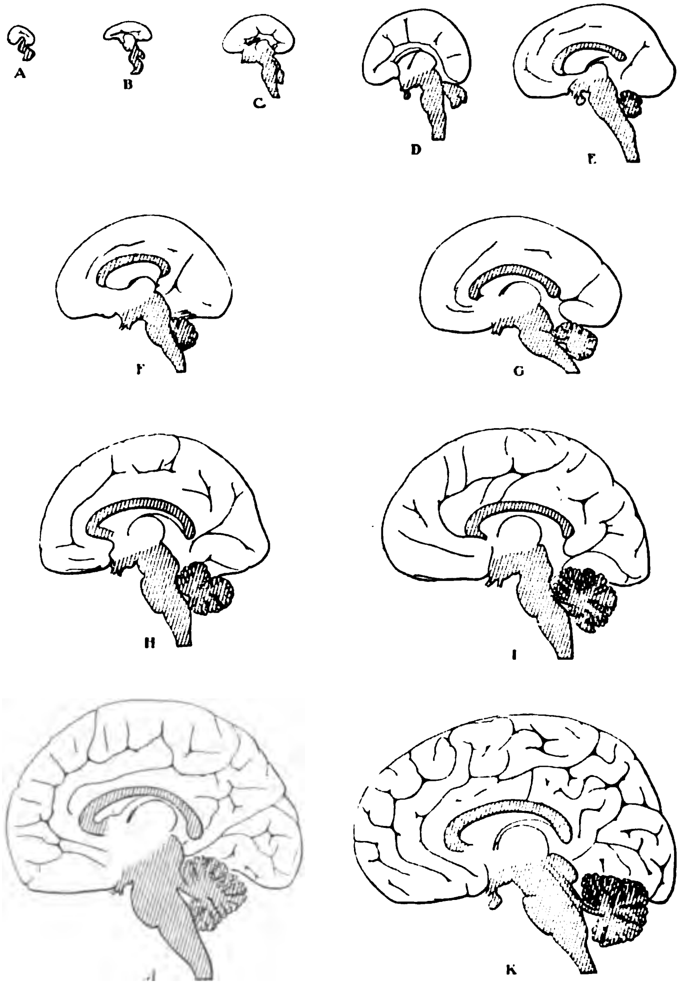


Fig. 37 A series of midsagittal tracings of the brain and brain stem. Each figure represents an average brain in each 5-cm. crown-heel interval. A, ca. 4 cm. C H length. B, ca. 7.5 cm. CH length. C, ca. 2.5 cm. C H length. D, ca. 17.5 cm. C H length. E, ca. 22.5 cm. C H length. F, ca. 27.5 cm. C H length. G, ca. 32.5 cm. C H length. H, ca. 37.5 cm. C H length. I, ca. 42.5 cm. C H length. J, ca. 47.5 cm. C H length. K, ca. 52.5 cm. C H length.

temporal diameter are practically identical. They occupy the same characteristic intermediate position between the cerebellum and the brain stem and spinal cord absolute growth curves. The rate of growth of the fronto-occipital diameter, when calculated from 5-cm. C H intervals (fig. 25, curves I and II) and also when calculated for age in fetal months (fig. 27, curves I and II), portrays an intermediate percentage increment curve lying between the cerebellum above and the brain stem below. The formulae of the fronto-occipital length and the temporal diameter (table 43) likewise show a characteristic grouping of the hemispheres to the general formula: $Y = aX + b$, in which Y is the fronto-occipital length or the temporal diameter in cm., X is the crown-heel length in cm., and a and b are constants determined for the two formulae.

Cerebral growth in volume shows a steady and relatively slow increase before the sixth fetal month and then a constant but more rapid increase from that time until birth. This is indicated by the right hemisphere volume, left hemisphere volume, and both hemisphere volume (figs. 4, 5, and 6, respectively). When calculated against crown-heel length and reduced to percentage basis (fig. 30), the right hemisphere volume, left hemisphere volume, and the volume of both hemispheres (curves IV, V, and VI, respectively), as well as the absolute curves of the central nervous system and the total brain volume (curves I and II, respectively), fall practically upon one another. The cerebellum volume curve lies below and the brain stem and spinal cord volume curve above the curves dominated by the factor of cerebral growth. Upon inspection of the curve of both hemisphere volume when calculated against time in fetal months and reduced to a percentage basis (fig. 36, curve II), a similar central grouping between the cerebellum volume, the brain stem volume, and spinal cord volume is observed. Turning to the figures upon the rate of growth of the cerebrum, which is determined for 5-cm. intervals (fig. 26, curves IV, V, and VI) and for age in fetal months (fig. 28, curve V), one observes the unswerving tendency of the cerebral growth to proceed faster before the sixth month and slower thereafter.

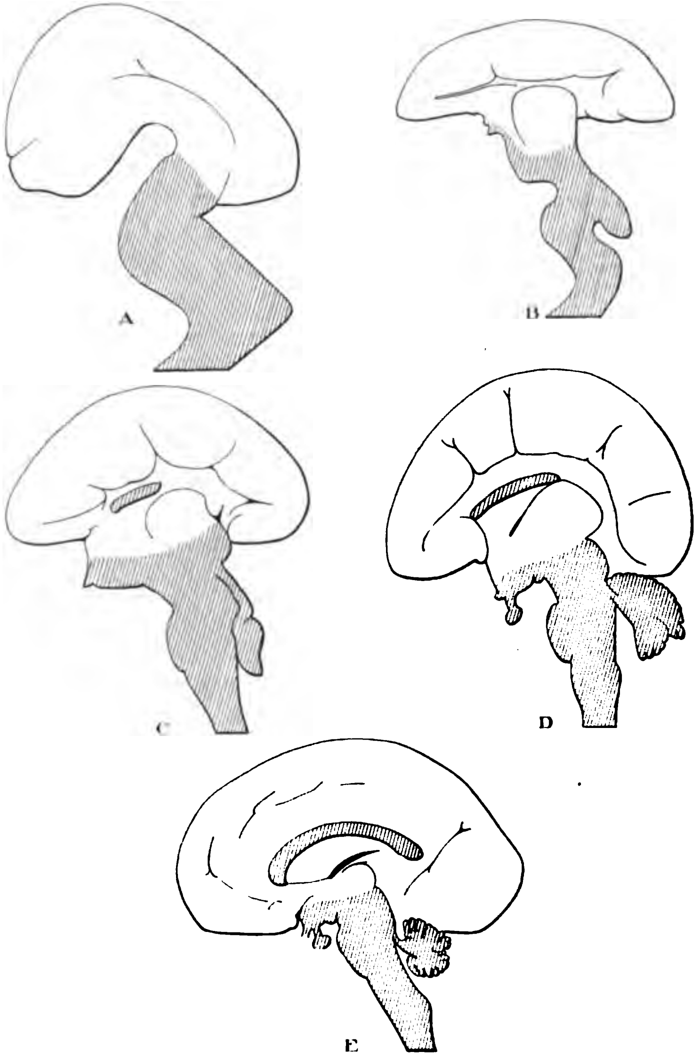
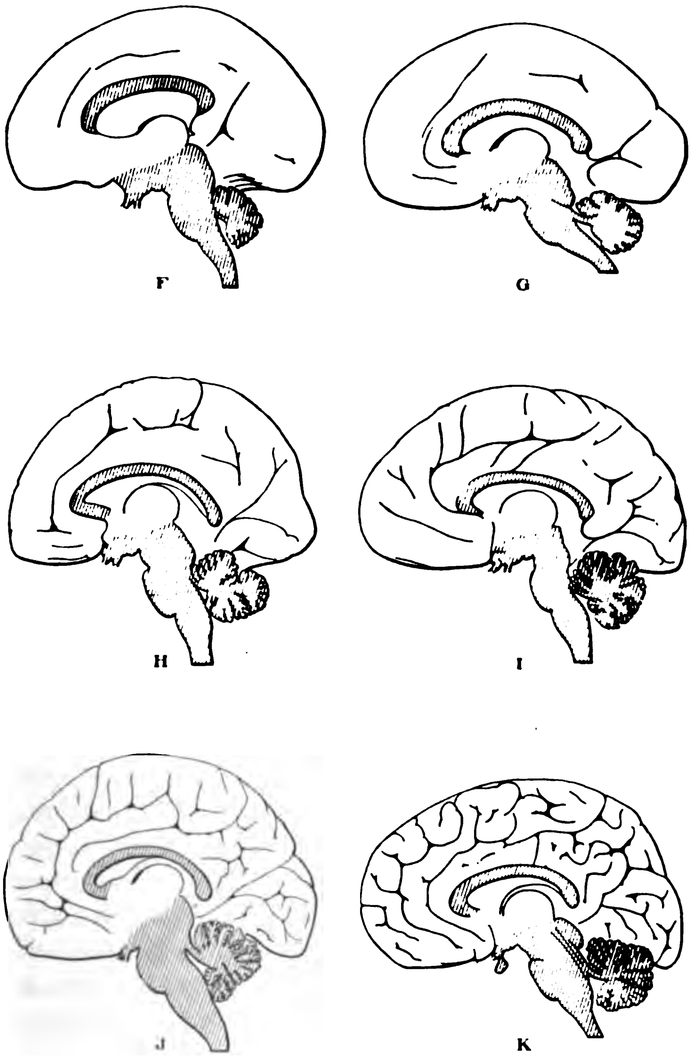


Fig. 38 A series of midsagittal tracings (of the specimens shown in figure 35) drawn to a standard fronto-occipital length. A, ca. 4 cm. C H length. B, ca. 7.5 cm. C H length. C, ca. 12.5 cm. C H length. D, ca. 17.5 cm. C H length.



E, ca. 22.5 cm. C H length. F, ca. 27.5 cm. C H length. G, ca. 32.5 cm. C H length. H, ca. 37.5 cm. C H length. I, ca. 42.5 cm. C H length. J, ca. 47.5 cm. C H length. K, ca. 52.5 cm. C H length.

The volumetric formulae of the right hemisphere volume, left hemisphere volume, and both hemisphere volume (table 43) are all expressed by the simple formula:

$$Y = (aX)^b$$

in which Y is the value to be determined in cc.; X, the crown-heel length in cm., and a and b are constants for the respective volumes.

Brain stem and spinal cord growth. The growth of the brain stem and spinal cord, as shown by curves of absolute linear dimensions and absolute volumes, represents a second definite type of growth in the central nervous system. It is characterized by a relatively rapid absolute and relative increase previous to the sixth fetal month and a slow increase during the last four months of intra-uterine life.

The linear determinations showing this type of growth are the frontospinal length, the spinal cord length, and the brain-cord length. When plotted against crown-heel length in centimeters and reduced to percentages of new-born values (fig. 29, curves VII, VIII, and IX) these three curves approximate one another and ascend more rapidly prior to the sixth fetal month than they do in the last four months. They are distinctly separated from the cerebral type of growth and, when calculated in fetal months and reduced to a per cent of the new-born (fig. 33, curves VII, VIII, and IX, respectively), they show even more clearly the almost identical path which they all follow. When calculated to time, they likewise show a rapid increase to the fifth fetal month and a comparatively slow one thereafter. The rates of growth of the brain stem and the spinal cord as shown by these three linear determinations can be observed equally well when taken for 5 cm. intervals (fig. 25, curves VII, VIII, and IX, respectively), or when calculated for age in fetal months (fig. 27, curves VII, V, and VI, respectively). The brain stem and spinal cord grow at a slower rate both relatively and absolutely than do all other brain parts during the last four months of fetal life.

The classification indicated by comparison of the absolute linear curves is substantiated by a glance at their respective formulae (table 43). The growths of most of the group are expressed by the general empirical formula:

$$Y = (aX)^b - c$$

in which Y is the brain-part value in cm., X is crown-heel length in cm., and a, b, and c are constants determined separately in each case for the frontal spinal length, spinal cord length, and the brain-cord length.

Two other straight-line measurements, one of the colliculi length and the other of the pons length, do not follow the typical brain stem and spinal cord type of growth for some unknown reason. They are straight-line curves and evidently express the growth of some specific factor rather than the growth of the brain stem of which they are a part.

The brain stem and cord growth are portrayed also in the curves of the spinal cord volume, the pons and medulla volume, and the midbrain volume. When calculated against crown-heel length (fig. 30, curves X, VIII, and XI, respectively), these volume curves show a relatively rapid absolute growth previous to the sixth month and a slow growth in the last four months of fetal life. They also approximate each other and fall definitely above the cerebral type of growth curve. They are practically identical when calculated against fetal months and reduced to a per cent of the new-born value (fig. 36, curves VI, IV and V, respectively). When the percentage increments of the spinal cord volume, the pons and medulla volume, and the midbrain volume are compared (either when calculated for 5-cm. C H intervals (fig. 26, curves X, VIII, and IX, respectively) or for age in fetal months (fig. 28, curves I, II, and III, respectively)), the distinctive types of the brain stem and spinal cord growth are observed. They show a slow rate of relative growth in the third month, which increases three-fold in rapidity in the fourth month. From this time until birth the growth rate decreases in rapidity so that these portions show a less rapid relative increase in the last three fetal months than does any other brain part.

The classification is indicated also by volumetric formulae (table 43) which can be expressed by the general equation:

$$Y = 0.01\,[(aX)^b + c]$$

in which Y is the value desired in cc., X is the crown-heel in cm., and a, b, and c, are constants determined for the spinal-cord volume, the pons and medulla volume, and the midbrain volume.

Cerebellum growth. Cerebellum growth, as shown by linear and volume absolute curves, proceeds slowly until the sixth fetal month, and from that time until birth outstrips all other growth activities in the central nervous system.

The lineal determinations expressing this type of growth are the vermis cerebelli length and the vermis cerebelli height (fig. 29, curves III and IV). If plotted against crown-heel length and reduced to per cents of their new-born values, they lie close together and ascend slowly at first and then more rapidly to birth in very shallow concave curves. They are decidedly different from all other straight-line absolute curves of the nervous system, resembling volumetric curves rather than lineal progressions. They show a similar definite classification when calculated against fetal months (fig. 33, curves III and IV). The rate of growth of the cerebellum, as shown by the percentage increment curves of the vermis cerebelli length and the vermis cerebelli height either when calculated for 5-cm. C H intervals (fig. 25, curves III and IV) or for age in fetal months (fig. 27, curves VIII and IX), reflect the cerebellum type of growth. During the last four fetal months the percentage increment of the vermis cerebelli length and the vermis cerebelli height is higher by 8 to 10 per cent than all other linear percentage increment curves of the central nervous system.

A consideration of the vermis cerebelli length and the vermis cerebelli height formulae (table 43) shows the volumetric tendency of these linear formulae. They can be expressed by the general empirical formula:

$$Y = 0.01\ (X^a + b)$$

in which Y is the value desired in cm., X is crown-heel in cm., and a and b are constants determined for both the vermis cerebelli length and the vermis cerebelli height.

The curve of the volume of the cerebellum is striking in character and demonstrates the slow growth of the structure prior to the sixth fetal month and the tremendously rapid increment from that time until birth. When calculated against crown-heel length (fig. 30, curve VII), and also when calculated against time in fetal months (fig. 36, curve III), the distinct character of the cerebellum volume is apparent. The formula of the growth curve of the cerebellum (table 43) is also characteristic, although it falls with the same general formula as the brain stem and spinal-cord volume, viz.:

$$Y = 0.01\,[(aX)^b + c]$$

However, it will be noticed that the *b* factor is 4.9 in the case of the cerebellum volume. This means that while the spinal cord volume, midbrain volume, and the pons and medulla volume are increasing practically as the cube and therefore like typical volume curves, the cerebellum volume is growing at a rate approaching the ninth power of the body length. The percentage increment of the cerebellum volume both when calculated for 5-cm. C H intervals (fig. 26, curve VII) or for age in fetal months (fig. 28, curve IV), also demonstrates a specific type of growth and shows the great increment of the part in the later fetal months as indicated by other measurements of cerebellum growth.

Compound growth. Compound growth indicates a summation of two or all types of growth in the central nervous system. It is typified by the volume and weight of the encephalon and the central nervous system volume. It is dominated by the growth of the cerebrum, since the cerebrum ranges between 85 and 95 per cent of the encephalon throughout fetal life. The rates of growth of the compound growth curves, as shown by percentage increments calculated for 5-cm. intervals (figs. 26, curves I, II, and III) and for fetal months (fig. 28, curves VI, VII and VIII), approximate the growth rate of the cerebrum. However, it will be noticed that in the early fetal months the rate of growth is not quite so high, due to the slow development of the other brain parts at this period.

The volumetric formulae (of the type here presented) of the central nervous system, the entire brain volume, and the encephalon weight require a third constant in their expression, while the volume of the cerebral hemispheres can be expressed mathematically with two constants. The general empirical formula of compound growth can be expressed:

$$Y = (aX)^b + c$$

in which Y is the volume of the encephalon or entire central nervous system in cc., X is the crown-heel length in cm., and a, b, and c are constants separately determined for the entire brain volume and the central nervous system volume.

The significance of the relation between lineal and volumetric dimensions in the growth of the parts of the brain. The classification of the types of growth of the central nervous system is shown by both the volume and linear curves. For instance, both the volume curve of the cerebellum and the linear measurements of the vermis cerebelli length and the vermis cerebelli height indicate the characteristic cerebellum type of growth. It is logical that there should be a definite relation between the linear and the volume measurements of a brain part. It is also evident that the length of a brain part when it is cubed should form a curve identical in type and constant in relationship to the corresponding volume curve, provided that no additional factor, other than that which influences the growth in the linear dimensions, influences the growth in volume. Such a relationship actually exists between the formulae of the linear cerebellum curves and the formula of the cerebellum curve of volume. The formula for the cerebellum length when cubed is practically identical to the formula of the cerebellum volume. This relationship is seen somewhat better when those values are based on the cube of the body length as modified by three constants rather than by a formula based on the body length raised to a fractional exponent. The first formula is expressed below:

$$\text{Cerebellum volume (cc.)} = [0.01\ (0.073\ \text{Vermis cerebelli length (cm.)} + 2.85)^3]^3$$

Likewise, the formula of the cerebellum height when cubed and multiplied by the constant 2.13 is practically identical with the formula of the cerebellum volume:

$$\text{Cerebellum volume (cc.)} + [0.01\ (0.07\ \text{Vermis cerebelli height (cm.)} = 2.\underline{4}5)^3]^3$$

These indicate that the cerebellum volume is growing at relatively the same rate as are its vertical and horizontal diameters. The growth of the cerebellum must be controlled, therefore, by factors which act alike upon the entire cerebellum.

The formulae of the fronto-occipital length and the temporal diameter when cubed bear no relation to the cerebrum volume which may be expressed by a simple constant, and the same holds true of the spinal cord length when cubed. It is obvious, therefore, that in all other brain parts except the cerebellum there must be more than one factor influencing growth which act differently on the volumetric and linear growth.

The per cent of the brain parts and the spinal cord of the encephalon. The per cent which the various brain parts and the spinal cord form of the encephalon at each fetal month can be observed by a glance at table 40 and at figures 7, 11, 15, 18, 22, and 38. Table 40 tabulates the per cent which a respective volume of a brain part or of the spinal cord forms of the encephalon. Figures 7, 11, 15, 18, and 22 demonstrate graphically the per cent which the pons and medulla, midbrain, and the spinal cord, respectively, form of the encephalon volume. Figure 38 represents a series of composite midsagittal sections which are based upon average measurements and which represent therefore a typical fetal brain for the 5-cm. C. H. interval indicated. For purpose of comparison, a magnification of each individual figure was used. To obtain this magnification, the ratio of the respective fronto-occipital diameters to the fronto-occipital diameter of the newborn was used. The detailed results of both figures and the table have been presented in the body of this paper. Taken in toto, the evidence shows conclusively: first, the high percentages which the pons and medulla, midbrain, and the spinal cord volumes form of the encephalon volume from the second to the fifth fetal month; second, the increased percentages which the cerebellum volume forms of the encephalon volume in the last three fetal months, and, third, the predominating percentages which the volume of the cerebral hemispheres form of the encephalon volume at all times, rising to its maximum per cent (94.2 per cent) in the sixth fetal month.

SUMMARY

I. The growth of the central nervous system in the fetal period is similar in general character to the growth of the other viscera and of the major parts of the body in this period.

II. An analysis of data on the volume and dimensions of the central nervous system in the fetal period shows four distinct subtypes or varieties of growth. These are:

1. The cerebral subtype, which is characterized by, *a*) a steady and relatively slow increase in volume from the second to the beginning of the sixth fetal month and a constant and more rapid increase from this time to birth, and, *b*) by a steady and constant growth in linear dimensions from the second fetal month to birth.
2. The brain stem and cord subtype, which shows a much more rapid growth from the second to the end of the fifth fetal month than it does in the last five months of fetal life.
3. The cerebellum subtype, which proceeds very slowly from the second to the end of the fifth fetal month and then increases tremendously from the sixth month to birth.
4. The compound subtype, which represents the combined effect of two or three or all of the above varieties, predominated by the cerebral subtype.

III. The factors which control the various subtypes of growth in the central nervous system may influence the volumetric and linear determinations of a respective brain part in two ways: 1) the factors may act differently upon the volumetric and linear values as they do in the case of the cerebral growth, brain stem, and cord growth, and in compound growth, or, 2) they may act in the same manner as they do in the case of the cerebellum subtype of growth.

IV. An estimation of the percentages which the cerebrum, cerebellum, and the brain stem form of the encephalon at the various periods of fetal life offers a means of comparison of the relative growth of these parts. The percentages which the brain stem and the spinal cord form of the encephalon are relatively high from the second to the fifth fetal month; the per cent which the cerebellum form of the encephalon is at its height in the last three fetal months, while the per cent which the hemispheres form of the encephalon reaches its maximum in the sixth fetal month.

V. The four subtypes of growth of the central nervous system may be clearly expressed by a classification of the empirical formulae of the growth curves of the various parts as follows:

1. *Cerebral growth:*
    - *a.* General linear formula: $Y = aX \pm b$.
    - *b.* Specific linear formulae:
        - *a′.* Fronto-occipital diameter: $Y = 0.175\ X + 0.25$.
        - *b′.* Temporal diameter: $Y = 0.138\ X + 0.3$.
    - *c.* General volumetric formula: $Y = (aX)^{b}$.
    - *d.* Specific volumetric formulae:
        - *a′.* Right hemisphere volume: $Y = (0.1\ X)^{3.13}$.
        - *b′.* Left hemisphere volume: $Y = (0.105\ X)^{3.04}$.
        - *c′.* Both hemisphere volume: $Y = (0.12\ X)^{3.19}$.
2. *Brain stem and cord growth:*
    - *a.* General linear formula: $Y = (aX)^{b} - c$.
    - *b.* Specific linear formulae:
        - *a′.* Fronto-spinal length: $Y = (2.0\ X)^{.47} - 2.2$.
        - *b′.* Spinal cord length: $Y = (10.0\ X)^{.467} - 4.0$.
        - *c′.* Brain cord length: $Y = (10.0\ X)^{.514} - 4.0$.
    - *c.* General volumetric formula: $Y = 0.01\ [(aX)^{b} + c]$.
    - *d.* Specific volumetric formulae:
        - *a′.* Spinal cord volume: $Y = 0.01\ [(0.17\ X)^{2.57} + 11.0]$.
        - *b′.* Pons and medulla volume: $Y = 0.01\ [(0.2\ X)^{2.67} + 20.0]$.
        - *c′.* Midbrain volume: $Y = 0.01\ [(0.168\ X)^{2.56} + 12.0]$.
3. *Cerebellum growth:*
    - *a.* General linear formula: $Y = 0.01\ [X^{a} + b]$.
    - *b.* Specific linear formulae:
        - *a′.* Vermis cerebelli length: $Y = 0.01\ [X^{1.41} + 0.15]$.
        - *b′.* Vermis cerebelli height: $Y = 0.01\ [X^{1.37}]$.

- *c*. General volumetric formula: $Y = 0.01\ [(aX)^{b} + c]$.
- *d*. Specific volumetric formula:
  - *a′*. Cerebellum volume: $Y = 0.01\ [(0.095\ X)^{4.9} + 20.0]$.

4. *Compound growth:*
   - *a*. General volumetric formula: $Y = (aX)^{b} + c$.
   - *b*. Specific volumetric formulae:
     - *a′*. Encephalon volume: $Y = (0.125\ X)^{3.16} + 1.5$.
     - *b′*. Brain and spinal cord volume: $Y = (0.114\ X)^{3.34} + 2.0$.
     - *c′*. Encephalon weight by literature: $Y = (0.13\ X)^{3.19} + 1.0$.

(In all of the above formulae, Y is the volume or length of the part under consideration (in cm. or cc.), X is the crown-heel or total length of the body in cm., and a, b, and c are empirically determined constants.)

BIBLIOGRAPHY

ARNOVLJEVIČ, S. 1884 Das Alter, die Grössen und die Gewichtsbestimmungen der Fötalorgane beim menschlichen Fötus. Diss., München.

BISCHOFF, E. 1863 Einige Gewichts und Trockenbestimmung der Organe dese menschlichen Körpers. Zeitschr. f. rationelle Med., III Reihe, Bd. 20.

BISCHOFF, T. L. W. 1880 Das Hirngewicht des Menschen. Bonn.

BOYD, R. 1861 Tables of the weights of the human body and internal organs in the sane and insane at various ages, arranged from 2614 post-mortem examinations. Phil. Trans. Roy. Soc. London, vol. 151, pt. 1, pp. 241–252.

BRANDT, E. 1886 Das Alter, die Grössen und Gewichtsbestimmungen der Foetalorgane beim menschlichen Foetus. Diss., München, 30 pp.

BUCHSTAB, H. 1884 (Material on the question of the weight and volume of the brain.) (Russian Diss. St. Petersburg.)

CALKINS, L. A. 1921 The growth of the external dimensions of the human body in the fetal period and its expression by empirical formulae. Report of meeting of Am. Assoc. of Anat., Mar. 24–26, 1921.

DANIELBEKOFF, A. 1885 Data on the weight and the volume of the brain and the spinal cord in children of both sexes under one year of age. (Russian.) Diss., St. Petersburg, 24 and II pp.

DUNN, H. L. 1921 The growth of the brain and the spinal cord in the human fetus and its expression by empirical formulae. Anat. Rec., vol. 21, p. 55 (Abstract).

GIESE, 1898 Diss., St. Petersburg. (Quoted from Gundobin; Die Besonderheiten des Kindesalters, pp. 481 et seq.)

HANDMANN, E. 1906 Über das Hirngewicht des Menschen auf Grund von 1414 im pathologischen Institute zu Leipzig vorgenommen Hirnwägungen. Arch. f. Anat. u. Physiol., Anat. Abt.

HATAI, S. 1911 An interpretation of growth curves from a dynamical standpoint. Anat. Rec., vol. 5. pp. 373–382.

HRDLIČKA 1906 The physical changes in human and other brains collected under different conditions and preserved in various formalin preparations. Proc. U. S. Nat. Museum. vol. 30, pp. 245–320.

HUSCHKE, E. 1854 Schaedel, Hirn und Seele des Menschen und der Thiere nach Alter, Geschlecht und Race. Dargestellt nach neuen Methoden und Untersuchungen. Jena.

JACKSON, C. M. 1909 On the prenatal growth of the human body and the relative growth of the various organs and parts. Am. Jour. Anat., vol. 9, pp. 117–165.

KING, H. D. 1910 The effects of various fixatives on the brain of the albino rat, with an account of a method of preparing this material for a study of the cells in the cortex. Anat. Rec., vol. 4, pp. 213–239.

MICHAELIS, P. 1906 Das Hirngewicht des Kindes. Monatsschr. f. Kinderheilk., Bd. 6, S. 9–26.

PFISTER, H. 1903 Zur Anthropologie des Rückenmarks. Neurologisches Centralblatt. Bd. 22, S. 757–762; 819–824.

RUDINGER 1877 Vorläufige Mittheilungen über die Unterschiede der Grosshirnwindung nach dem Geschlecht beim Foetus and Neugeborenen mit Berücksichtung der angeborenen Brachycephalie und Dolichocephalie. Beitr. zur Anthropol. u. Urges. Bayerns, Bd. 1, S. 24.

RUDOLPH, O. 1914 Untersuchungen über Hirngewicht, Hirnvolume, und Schädelkapazität. Beitr. z. path. Anat., Bd. 58.

SCAMMON, R. E. 1921 On the growth in weight of the human body and its various parts and organs in the fetal period, and its expression by empirical formulae. Anat. Rec., vol. 21, p. 79 (abstract).

SCHULTZ, A. H. 1919 Changes in fetuses due to formalin preservation. Am. Jour. Phys. Anthrop., vol. 2, no. 1, pp. 35–41.

VALTORTA, F. 1909 Richerche sullo svilúppo dei visceri del feto. La individualità nel neonato. Ann. Ostet. e Ginècol., I, XXXI, 673–713.

VOLPIN, L. L. 1902 (Weight determinations on the growth of the brain in children.) Diss., St. Petersburg, 110 pp. (Russian). (Rev: Jahresb. f. Anat. u. Ent., 1903, Abth. 3, S. 640–645.)

WELCKER, H., UND BRANDT, A. 1903 Gewichtswerte der Körperorgane bei dem Menschen und den Tieren. Arch. f. Anthropol., Bd. 28.

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THE INTER-RELATION OF THE THYREOID AND HYPOPHYSIS IN THE GROWTH AND DEVELOPMENT OF FROG LARVAE

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In attempts at establishing the function of the ductless glands, investigators are limited to relatively a few kinds of experiments. One can administer a particular gland to an animal or transplant the gland into the animal in the hope of bringing about a condition wherein the subject receives more than the normal amount of the hormone being studied. One can extirpate a gland from an animal and then administer to it preparations of the type of gland removed, and one can remove a gland of one type and administer prepared glands of another type. Still further, various combinations and modifications of the above kinds of experiments can be attempted. The unsatisfactory elements in ductless gland investigations are difficulties of controlling the experiments and the greater difficulties of interpretation of the results.

In administering ductless glands one must admit that the preparations are abnormal to begin with. The glands used are dead and only hormones that are relatively stable can be preserved. Even here we have no absolutely certain method of checking our findings and must usually reason by inference and deduction in the interpretation of results. Further, as has previously been pointed out, experiments with prepared glandular substances are more often pharmacological than physiological, especially when extracts obtained by any agent other than physiological salt solution are used. The body itself can hardly be expected to prepare from its own glands extracts requiring strong sulphuric acid, ether, acetone, alcohol and so forth. It is one thing to bring about certain reactions by the use of such preparations and quite another to prove that similar reactions are normally brought about by the living gland within the animal's body. However, we are on reasonably safe ground when we can, by administering preparations of a particular gland, prevent the occurrence of symptoms that would otherwise result from extirpation of the gland in question.

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Transplanting a ductless gland into an otherwise normal animal would seem at first sight to be a method whereby hypersecretion could be brought about and the animal thus provided with more than the normal amount of hormones from the gland in question, but a usually ignored fact is that the host exerts a controlling influence upon the transplant, as well as the transplant upon the host, so that an equilibrium often results. We have transplanted thyreoids into embryos for example (Hoskins and Hoskins '19a) and observed later that they "took," so that the animals possessed an anatomical excess of thyreoid tissue, but were apparently able to regulate the amount of thyreoid hormones secreted by their own and the transplanted glands, because no symptoms of "hyperthyreoidism" resulted.

After a ductless gland has been extirpated there is often a considerable readjustment among the other structures of the body, so that of the resulting symptoms, some are due directly to the loss of the gland removed while others are caused only indirectly by the removal, and it is usually not possible to distinguish between these categories. Metabolic processes are so complex that phenomena occurring together may be merely concomitantly and not causally related. As an example of this complexity we may consider the results of thyreoidectomy wherein there occurs a physiological (perhaps pathological) hyperplasia of the hypophysis, so that the resulting symptoms are brought about presumably both by the thyreoid deficiency and by hyper-activity of the pituitary, and it is very difficult to tell from such an experiment the normal function of the thyreoid. At best in such cases we can only say that there is some relation between certain processes and the gland in question.

METHODS AND MATERIAL

In the following experiments with hypophysis feeding we have administered a commercial preparation of the anterior lobe of beef pituitary (Armour & Co.) to otherwise normal larvae of Rana sylvatica, and to larvae of the same species from which the thyreoid had been removed in the embryonic stage before it could have begun to function. This preparation consists of dry substance of the anterior lobes of the hypophysis, put up in tablets of milk sugar. The tablets are composed of two grains of bovine anterior lobe pituitary substance dried in a vacuum (representing 10 grains fresh gland) mixed with three grains of milk sugar. A. C. Henderson of the Armour and Company laboratory states in a personal communication of June 4, 1919, "Our anterior pituitary substance is made from carefully selected material and is, we might say, entirely without iodin; at least there is not any more than would be found in muscle substance, which means practically none at all. It is absolutely free from thyreoid tissue."

Dr. E. C. Kendall of the Mayo Foundation, who kindly analysed this material for us, reported that each tablet of two grains of dried anterior pituitary substance contains .0035 mg. of iodine, either organic or inorganic, a content of one part in 40,000 which would be 1:200,000 in the fresh gland. Dr. Kendall is of the opinion that the iodine present is soluble, and if so, considering the amount of water in the larger aquaria, the dilution of the iodine was 1:570,000,000, a concentration much less than is necessary to stimulate metabolism in tadpoles (Swingle '19) if inorganic iodine is used.

Even if the iodine did not go into solution, only a very small fraction of .0035 mg. of it was ingested by each larva in one dose, yet in most cases an effect was noticeable within twenty-four hours after the first dose was administered.

The active principle of the hypophysis, whether it contains iodine or not, apparently is soluble, as shown by the fact that the thyreoidless larvae continued to develop after their jaws began to metamorphose, and they were thus compelled to stop eating the tablets.

In several different experiments, most of which we have not yet described, it was found that eggs collected early in the season developed into larger animals than those taken later, or taken early and kept for a time in cold storage before being used.

In each experiment the controls and the experimental larvae were of the same age and size and were taken from the same mass of eggs.

In addition to the hypophysis tablets the experimental larvae received Spirogyra in abundance, and the controls received milk sugar and Spirogyra. The water in the aquaria was changed the day after each administration of the tablets or sugar.

The larvae were under daily observation and were measured from time to time as indicated.

Before being autopsied, the animals were fixed in Bouin's fluid.

The experiments were performed in the Anatomy department of the University of Pittsburgh.

I. Effects of administering a preparation of the anterior lobe of the pituitary to normal larvae.

Experiment 1. April 27, 1919.

Fifteen animals were selected for hypophysis feeding and 15 of the same size kept for controls. Each set was kept in one aquarium in which they had an abundant supply of normal food. In addition to this food, one pituitary tablet was given daily to the experimental group, while the controls received milk sugar. The treatment was continued from April 27 to May 13, 1919, making a total of 17 tablets given in this way.

Experiment 2. April 28.

Three sets of 13 animals each were chosen for this experiment. Those of the first group (A) were taken at intervals from the aquarium in which they were receiving their normal food, and placed in a small jar of water, containing one pituitary tablet. They were left in this jar for 24 hours, during which time they ate a portion of the tablet. Five treatments were given on the following dates: April 28-29, May 5-6, May 13-14, May 15-16, May 22-23.

The second group of tadpoles in this experiment (2B) was used at first as a control for group 2A, to make sure that the effects observed in the latter were not due to the fact that the animals were temporarily deprived of their ordinary food. When group 2A was placed in the aquarium containing the pituitary tablet, group B was also taken from its aquarium and put in a small jar containing water and a few cracker crumbs. The animals were left there as long as those of group A were feeding on the pituitary substance, and then returned to the aquarium, where they received normal food. As no effect resulted from these periods of light feeding, the control was discontinued and the animals used in another way. They were left in a small jar containing water and a pituitary tablet for periods of one hour each. Nine such doses were given between May second and sixteenth.

The third group of tadpoles (C) for this experiment was composed of normal animals kept on an ordinary diet of leaves and algae.

It will be seen that in these experiments care has been taken to avoid starving the animals. In number 1, an abundant supply of normal food was always present with the hypophysis substance, and the animals ate freely of it as well as of the tablets. In 2A the effect of 24 hours at a time on light diet was checked by a control, as above described; and in 2B the periods of removal from the normal food were too short to have any effect in themselves. The effect that the sugar content of the tablets might have had was checked by the giving of milk sugar to the control larvae.

RESULTS OF EXPERIMENTS

Experiment 1.

At the beginning of this experiment the animals measured as follows:

15 for hypophysis feeding:

Body length, 9-10 mm., average 9.4 mm.
Total length 20-23 mm., average 21.1 mm.

15 for controls:

Body length, 9-10 mm., average 9.4 mm.
Total length, 20-22.5 mm., average 20.7 mm.

The first noticeable effect of the hypophysis feeding was a marked wasting of the bodies of the animals, which gave them the appearance of starved tadpoles. As has been said, the possibility of starvation has been carefully excluded from this experiment, and this emaciation differs from that produced by starvation in the time of its appearance. A normal tadpole kept without food does not show noticeable changes in form for four or five days, and is not strikingly wasted until several days later. The emaciation following hypophysis feeding is seen within 48 hours after the experiment is begun. Within a few days, however, the animals seem to recover from the first effect of the dose, and their bodies fill out again to the normal form. While the wasted appearance of the body lasts, the animals are sluggish in their behavior. Later, however, they become more lively than the normal tadpoles, and show a high degree of irritability, so that the slightest jarring of the aquarium starts them all to swimming about very actively.

By May 3, 1919, one week after the beginning of the experiment, the measurements taken showed that the hypophysis-fed animals were growing faster than the controls. These measurements are:

Hypophysis-fed—B. 10-12 mm., aver. 10.5; total 25-29 mm., aver. 26.7 mm.

Controls—B. 9-10 mm., aver. 9.8; total 20.5-23 mm., aver. 21.9 mm.

The greater length of the tails of the hypophysis-fed animals is particularly noticeable. In them the tail made up 61 per cent of the total length, while in the normal tadpoles it was only 55 per cent of the whole.

On May 8th the measurements showed still greater difference between the two groups of animals, as follows:

Hypophysis-fed—B. 10-12.5 mm., aver. 11 mm. Total 28-36 mm., aver. 31.5 mm.

Controls—B. 9-11 mm., aver. 10 mm. Total 20.5-25 mm., aver. 22.5 mm.

In addition to the size difference. which is largely due to the unusual length of tail, marked changes in appearance may be seen in the hypophysis-fed animals. Figure 1, drawn four days later, represents a tadpole of the average size on May 8th (Body 11 mm. Total 32 mm.) and a normal but older tadpole of the same total length is shown in figure 2. The hypophysis-fed specimen shows a decided approach to the adult form. The body has become thinner both laterally and dorso-ventrally, showing that the intestine has been reduced in length. The anal canal has also shortened, the legs are well developed, and the pigmentation is like that of a frog. All these changes show that the animal has passed its maximum size and begun metamorphosis. The normal animal of the same length shows none of these signs of approaching metamorphosis. Its intestine and anal canal have not begun to shorten, its hind legs are represented by buds of tissue, and it retains the larval pigmentation. Figures 1 and 2 also illustrate the abnormal relation of tail and body in the hypophysis-fed specimen.

On May 13th all the hypophysis-fed tadpoles in this experiment were undergoing metamorphosis. The measurements showed a decrease in length, the approach to the adult form was noticeable in all the animals, and one tadpole had three legs. Five tadpoles, all of which had passed their maximum size, were found dead on this day, and the hypoyhysis feeding was discontinued.

No fully developed frogs were obtained from this experiment, though several members of the group reached a condition just short of the frog stage. Their bodies were frog-like, but a stump of tail of a few millimeters remained. The animals seemed to have been somewhat weakened by the treatment, so that they could not survive metamorphosis. Those that reached the stage at which they were able to leave the water had undergone a great shrinkage, but died before their tails had entirely disappeared. There is, of course, a reduction of the size of a normal animal in passing from the larval to the adult stage, but it is not quite so great as that seen in hypophysis-fed tadpoles. One member of this group died on May 14, and five more on May 20. All of these had four legs, and the tails had begun to shrink. On May 25 an animal which was already leaving the water died, and on May 30 the last two were killed. One of these, also, had practically completed metamorphosis, and was leaving the water. The other still had a considerable stump of tail.

During this time (May 13-30) the control animals had developed much more slowly and did not reach their maximum length (B. 15, total 40 mm.) until early in June. The representative normal tadpole preserved on May 20 still retains the larval form of body and the hind limbs are but slightly developed, the digits of the foot being barely distinguishable. No completely metamorphosed frogs were found until June 9th, ten days later than the day on which the last of the hypophysis-fed animals left the water. On June 17th, when the experiments were ended, one of the normal animals was practically in the frog condition, but others were no farther advanced than the hypophysis-fed animals had been on May 13.

The precocious metamorphosis of hypophysis-fed tadpoles naturally gives rise to abnormally small frogs. The first of this group to reach the adult condition is shown in figure 3, and the first control frog in figure 4 (Plate II). The hypophysis-fed animal is normal in appearance except for its size. Its length (fixed) was only 8.4 mm., while that of the normal frog (somewhat below the normal average) was 10.4 mm. (fixed). The minimum length of the other hypophysis-fed frogs from this group was 8 mm.

Group 2A

It was in this group that the effects of hypophysis feeding were most marked. The animals were fed for 24 hours at a time on an exclusive diet of the pituitary tablets. The toxic effect of the first dose was very noticeable. The animals became much emaciated, and floated at the surface of the water, often on their backs. They remained in this condition for several days, and although they ultimately regained their normal shape, their growth appeared to have received a check from which it did not entirely recover. There was no period when the animals of this group were larger than the controls. The disproportionate growth of the tails which was seen in experiment 1 was less marked in this group. In the interval between the first two doses (April 29-May 5) the average length of these tadpoles increased as follows: Body from 8.4 mm. to 8.8 mm.; total from

18.8 mm. to 21.5 mm. The control tadpoles, in the meantime, had grown from 8.5-18.9 to 10.5-22.4 (body and total length in mm.). The second dose, given May 5-6, had no toxic effect on the animals. Between May 6 and May 15, there was an increase of 1.2 mm. in their bodies and .9 mm. in their tails. On May 16 the effect of the feeding on the form and development of their bodies was clearly apparent. Figure 5 (Plate III) drawn at this date, is to be compared with figure 6, its control. The most noticeable abnormalities appear in the lateral view of the hypophysis-fed tadpole, from which may be seen that the intestines are already reduced, giving the animal a much smaller abdomen than is seen in the normal specimen. This shortening of the intestine is one of the later metamorphic changes in a normal animal, but occurs in hypophysis-fed tadpoles at a relatively early date, before the legs have developed to any very great extent. The legs of the animal shown in figure 5 do not correspond in their development to the condition of the intestine, but are much more advanced than the legs of the control (fig. 6), although the latter is considerably the larger of the two.

Between the dose of May 16 and that of May 22 the tadpoles increased very little in size. The average length on May 16 was: Body, 10 mm.; total, 23.6 mm.; and on May 22nd, Body, 10.5 mm.; total, 26.1 mm. This was their maximum length, and by May 26 the anal canal had shortened and metamorphosis had begun. Figure 7 shows the smallest animal of this stage of development which we obtained from any of these experiments. Although the body of this animal was only 8 mm. long, the reduced abdomen and anal canal, the well developed legs, and the pigmentation shows that it has already begun its metamorphosis.

As might be expected from the small size of the tadpoles of this group, the frogs developing from them were below the normal size. As in experiment 1, few survived metamorphosis. Those that did so range in size (fixed) from 7 to 10.5 mm., with an average length of 8.8 mm. They had an average volume of 0.15 cc. while the volume of the normal frogs was from 0.20 to 0.30 cc.

Group 2B

The animals in this experiment received less of the pituitary substance than those in either of the experiments just described, and the effect of the treatment was correspondingly smaller. There was no emaciation following the early doses, and the first result to be seen was a stimulation of the growth of the tail and hind legs, and the reduction of the abdomen, due to shortening of the intestine. By May 15, two weeks after the beginning of the experiment, the hypophysis-fed animals have, on the average, considerably longer tails than the controls, while the bodies remain practically the same in the two groups. The measurements taken on this date were: Hypophysis-fed: Body 11 mm., total 30.4 mm.; controls: body 10.9 mm., total 23.7 mm. Individuals may be found, however, among the hypophysis-fed animals, which show normal proportions as far as length is concerned. One of these is shown in figure 8, and is to be compared with figure 6, which represents a normal tadpole of the same length. The two show a striking contrast in outline, and in the development of their legs. Figure 8 is typical of the hypophysis-fed tadpoles at the time when the effects of the treatment are first noticeable. Comparison of this figure with figure 1 shows that although the animals of experiment 2B were stimulated by the hypophysis feeding, the changes indicative of metamorphosis took place more slowly than in the earlier experiments. Although most of the animals completed their metamorphosis early, a few showed very little effect from the feeding. An example is shown in figure 9, and its control in figure 10. The hypophysis-fed tadpole has a slightly longer tail than the normal one, and its legs are longer, but there is no external evidence of changes in the intestine. The two drawings were made on June 3, when many of the hypophysis-fed tadpoles of this group had completed their metamorphosis.

The frogs that developed from this group ranged in length from 9 to 11 mm., with an average length of 9.9 mm., as compared with the control frogs, which varied in length from 11 to 14 mm.

Discussion of Part I.

The effects of hypophysis feeding on normal young tadpoles may be divided into two groups: the toxic and the stimulating, as has been noted for thyreoid feeding. To the former group belongs the emaciation which immediately follows the first dose of the pituitary substance. Abderhalden '15 noted the toxic effect of pituitary extract. This effect is temporary, and does not recur after later doses. The animals appear to acquire a tolerance for the hypophysis substance. This may be the result of the repetition of doses, alone; or it may be that larger tadpoles have a greater resistance to the toxic effect. Late in the season an attempt was made to produce this effect on a normal tadpole, in order that a figure of this stage might be drawn. No such result was obtained, however, and this suggests that a tolerance may develop normally in the tadpoles with increasing size. No emaciation was produced in group 2B, the members of which were larger at the beginning of the experiment than those of the other group. In this case, however, the dose was small, and may have failed to affect the animals on that account.

2A. Although these animals recovered from the toxic effect of the first dose, their growth was considerably retarded.

The more interesting results of hypophysis-feeding are seen in various indications of stimulation. The most constant of these is the relatively rapid growth of the legs and tails of the treated animals. This effect is seen in animals which have received but a small amount of pituitary substance and are apparently not otherwise affected by the treatment, as well as in those which have had so much hypophysis that their general growth has been retarded.

The early shortening of the intestine occurs in almost all the animals, although a few in group 2B were not affected in this way. This result occurs relatively much earlier in the history of the hypophysis-fed tadpole than in that of the control; and hence it is more precocious than the development of the legs.

Moderate doses of the pituitary substance cause a stimulation of the growth of the body as well as of the legs and tail.

Metamorphosis as well as growth is hastened by pituitary feeding, in proportion to the amount of the substance administered. The process takes place relatively early in hypophysis-fed larvae, so that abnormally small frogs develop, and such larvae never become as large as the size attained later by the controls. The maximum length reached by any of our hypophysis-fed larvae was 36 mm. as compared with 40 mm. for the maximum of the controls. After metamorphosis the hypophysis-fed animals were from one-half to two-thirds as large as the control frogs, and were about three-fourths as long, as is described above.

While we do not believe that the iodine content in our preparation of pituitary was sufficient in itself to bring about the results obtained, such may be the case. But whether it is or not, the substance used was normal pituitary, and the results indicate a similarity of its action to that of thyreoid.

The normal presence of iodine in the hypophysis of mammals has been claimed by some previous investigators and denied by others. Thus Bauman '96 found no iodine in the human hypophysis, but Schnitzler '96 found a trace of it. Wells '97 reported finding 0.05 mg. of iodine in 1.22 grams of dried human hypophysis. Simpson and Hunter '09 could not find iodine in Armour and Company's ox pituitary preparation nor in the fresh pituitary of sheep following thyreoidectomy, but detected a trace in fresh normal sheep pituitary. They state that their method would detect iodine in the amount of 0.005 mg. in 1.2 grams of dried substance. Denis '11 could not find iodine in the human pituitary either before or after the administration of iodides. MacArthur '19 likewise did not find iodine in beef pituitary. Thus it appears that while iodine is present normally in the hypophysis of mammals, it may be at times either absent or in concentration too small to be detected by the technique employed.

Smith '18 states that anterior hypophysis substance and boiled lettuce fed to normal tadpoles causes a rapid growth just before the larvae begin to metamorphose and hastens this process, as compared to larvae to which liver and boiled lettuce is given. This difference in size is very much less than the variation within the two groups of larvae in Smith's experiments. and may not be of any significance. The liver may have had some effect upon the growth of the control larvae and if so they were not normal and the results obtained need confirmation. In our experiments the larvae to which anterior pituitary substance was administered began their metamorphosis before they had become as large as larvae of this species normally grow, and as a result, the frogs which were formed are smaller than normal. Since Smith did not mention any such effect on the size of his frogs, and since he did not notice any effects in the early part of his experiments, it is evident that the preparation of hypophysis used in his experiments was different in its action from our preparation.

II. Effects of administering a preparation of the anterior lobe of hypophysis to thyreoidless larvae.

For this experiment twelve thyreoidless larvae were selected as shown in the accompanying table. They varied in length from 42 to 53 mm. and in volume from 0.90 to 1.45 cc. Each was placed in a separate aquarium and treated as described under "Material and Methods." They were all kept under observation from 9 to 31 days, receiving from 9 to 21 doses of the hypophysis substance.

The normal control larvae, 50 in number (see Pl. IV.) had all passed the period of metamorphosis before most of the hypophysis feeding experiments were begun. These controls grew and developed normally and do not require description. They varied in maximum size before metamorphosis from a total length of 36 mm. to 41 mm. and volume of 0.50 cc. to 0.80 cc. After metamorphosis the control frogs varied from 13 mm. to 14 mm. in body length and from 0.30 to 0.45 cc. in volume. The hind legs were about 14 mm. long before metamorphosis and 15 to 18 mm. afterwards. It is easy to tell when metamorphosis proper is beginning by noting when the anal canal begins to shorten. Skeletal changes have already begun before this time, but there is no particular point in the skeletal growth that signifies metamorphic change, since the growth of the skeleton is at first very gradual. For a recent discussion of these normal changes see Hoskins and Hoskins '19b.

Thyreoidless larvae differ from normal larvae in many particulars as Allen, Hoskins and others have already described, and only a brief description will be given here. (See Pl. IV and VI.) These larvae that have had their thyreoid removed in the early embryonic stage, grow in volume and length more rapidly than normal, but if kept in normal conditions and given normal food, will not metamorphose at least for two years, although the control animals taken from the same eggs will change into frogs within four to eight weeks from the time the eggs are laid. These thyreoidless larvae ultimately become two to four times as large as normal larvae, but their skeleton shows little tendency to calcify or to ossify. Their legs develop only as rudimentary appendages a few millimeters in length.

It is interesting to note that Hahn '12 found four gigantic larvae occurring naturally in otherwise normal cultures of Rana esculenta, but unfortunately he did not study their thyreoids. It is highly probable, however, from Hahn's description that the thyreoids of his monsters were atrophied because the changes which he does describe are much like those occurring in thyreoidless larvae. He attributed their gigantism to hypertrophy of the pituitary.

In thyreoidectomized larvae, as in other animals, there results a hyperplasia of the pituitary after thyreoid removal, but the pituitary is not able to make good the loss of thyreoid secretions.

At the beginning of the hypophysis feeding the thyreoidless larvae resembled those previously described.

DESCRIPTION OF EXPERIMENTS

A. (Pl. V and table.)

This larva was about twice the size of a normal larva when the feeding began, its total length being 50 mm., nose-anus length 20 mm., hind limb buds 2 mm. and volume 1.50 cc. It received 18 daily doses of one-half tablet each, only a small amount of which it ate, as described above, and was observed for 20 days.

An effect of the medication was evident within 24 hours, at the end of which time the tail had shortened 10 per cent and the volume had diminished 12 per cent. The animal had become more active, as was true in all the following experiments after a single dose of hypophysis. If one approached or touched the aquaria, the larvae swam rapidly about and were difficult to catch, whereas before the medication began they were rather unresponsive to ordinary stiumli. The same effect was produced by Smith '16 by extirpating the hypophysis.

After two days the tail of animal A had decreased an additional 9 per cent in length, the volume had decreased 3 per cent, and the hind limbs had lengthened 25 per cent.

Between the sixth and eighth days the anal canal disappeared, the animal's body now being 17 mm. long.

Between the fourth and twelfth days the tail underwent a secondary growth period, giving the animal a total length of 48 mm. The hind limbs had grown to 15 mm., which is the average leg length of young frogs. The volume had, during this period, decreased to about two-thirds of the original. On the thirteenth day the left foreleg broke through the operculum. By this time the shape of the body and head was definitely that of a frog. The pigmentation and other skin changes also were those of normal metamorphosis. Two days later the other foreleg appeared. It came through the toughening skin with considerable difficulty. On the seventeenth day the total length was reduced again to 44 mm. The tail did not, however, have the appearance of a normal larval tail of the same length, being but half as wide dorso-ventrally and half as thick, showing evidence of impending disappearance. The body was still 17 mm. in length, but had become very much thinner. The hind limbs were 20 mm. long, were somewhat disproportionately thick, and were short also in relation to the size of the body. The volume was not measured at this time, but it appeared to be further decreased.

On the twentieth day of the experiment the animal was found dead in its aquarium, too much swollen for accurate measurement. It was much larger than a normal young frog, as was to be expected from the size of the larva at the beginning of the experiment. The animal had the shape and pigmentation of a frog, but a long narrow tail still persisted.

Autopsy showed the gastro-intestinal tract to be almost completely metamorphosed, the liver being greatly reduced in size and the gall-bladder enlarged as occurs normally; the gills were small and the lungs well differentiated, as were the kidneys, gonads and brain. In general it may be said that metamorphosis was between 80 and 90 per cent completed.

A. A. (Pl. V, VI, and table.)

At the beginning of the experiment the total length of this larva was 42 mm., the body length 19 mm., the hind limb buds 2 mm., and the volume was 0.98 cc. It was thus about a third larger than the average of the control larvae. It received 15 half-tablet doses of the pituitary substance during the first 18 days of the experiment, and was kept under observation for 31 days. In the first four days the tail increased 3 mm. in length, but the volume decreased to 0.75 cc., a loss of about 23 per cent, due partly to expulsion of intestinal contents.

By the sixth day the length had not changed, but the hind limbs had doubled in length and the volume had increased very slightly. By the ninth day the anal canal had shortened 3 mm., the hind legs had grown another mm. and the volume had decreased to about 66 per cent of the original.

On the next day the nose-anus length had still further decreased to about 74 per cent of the original and the hind legs had increased to 5.5 mm. On the twelfth day the total length was 41 mm., but the tail was very narrow dorso-ventrally, the volume had increased to 0.75 cc., the hind limbs were 6 mm. and the pigmentation was changing toward that of a frog.

Three days later the tail had increased 1 mm. and the hind limbs 3 mm., and the head and body were changing in shape toward that of a frog. On the nineteenth day the animal looked like a frog except for its long narrow tail. Both forelegs had appeared. The medication was stopped at this point.

Three days later the tail had shortened by 3 mm., the body length had increased 1 mm., the hind limbs were 16 mm. in length and the volume had been decreased to 51 per cent of the original. On the twenty-seventh day the tail had shortened again by 3 mm., and the hind limbs had increased in length another mm. The larva frequently tried to protrude its head from the water, so it was placed in an aquarium one end of which contained shallow water. From this time to the end of the experiment the animal, unless disturbed, remained in this end of the aquarium with its head out of water. On the thirty-first day the animal, which had practically become a frog, still had a very narrow and thin tail 20 mm. in length. Its volume had decreased to 36 per cent of the original, a decrease equal to the maximum loss suffered by a normal larva during metamorphosis. On this day while being examined it jumped from the observer's hand and was killed by the fall.

Autopsy showed a fully differentiated gastro-intestinal tract, the liver being even smaller than that of normal frogs, and the gall-bladder rather larger than normal. The gills had not been reduced in size as much as occurs in normal metamorphosis, although the lungs were well developed and functional. The kidneys appeared normal, the ovaries were quite large, and the brain was as fully differentiated as that of a young frog. Metamorphosis seemed to be complete save for the fact that the tail had not fully disappeared and the gills had not been very much reduced in size.

B. B. (Pl. V and table)

This animal had received but three doses of 2 grains each when it died on the fourth day. The total length had been reduced 4 per cent, its body length 7.5 per cent and its volume 33 per cent. Since the animal when measured on the previous day was almost as long as when the experiment began, it may have shrunken between the time it died and the time it was removed from its aquarium. A part of the loss in volume was due to discharge of fecal matter. At autopsy the viscera were still in the larval condition.

B. (Pl. V and table.)

This larva received eight daily doses of 1 grain and on the ninth day while being anaesthetized to be drawn, it died and was fixed. An effect of the pituitary substance was noticeable twenty-four hours after the experiment began, when it was seen that the entire length had changed from 46 to 47 mm., the body length from 20 to 20.5 mm., the hind limb from 1.5 to 2 mm., all signs of growth, but the volume had decreased from 1.30 to 1.15 cc.

On the next day the animal was the same length, but its volume had decreased to 1.10 cc. and the hind limbs had increased to 2.5 mm.

On the fourth day the tail had lengthened another mm., and the hind legs 0.5 mm., but the anal canal had decreased 1.5 mm., and the volume 0.10 cc., the latter being now 23 per cent less than at the beginning of the experiment. By the seventh day the anal canal had disappeared and the body was beginning to change in shape. On the ninth day the larva had decreased in total length to 47 mm., and in nose-anus length to 16 mm.

The volume was 0.85 cc. or about 65 per cent of the original. The hind limbs had grown to 7 mm. and the fore limbs beneath the operculum were 3.5 mm. long.

Autopsy showed that the gastro-intestinal tract was changed about half way to that of the frog stage. The liver had formed its three lobes, was being freed from the coil of gut which in the larval stage is embedded in it, and the gall-bladder had increased in size. The gills showed little change, but the lungs were large and air-containing. The kidneys and ovaries showed no peculiarities. The latter were large, but as Allen and we have shown, thyreoidless larvae develop large gonads. The brain showed differentiation beyond that of the thyreoidless larval type.

C. (Pl. V and table.)

This animal reacted in about the same way as A. It received 18 one-half tablet daily doses of the anterior pituitary substance and was found dead in the aquarium on the twentieth day, from drowning or other cause.

Within 24 hours after the first dose the larva began to decrease in volume. As in most of the experiments the tail increased in length at first, but rapidly decreased in size, and after 10 days, in length also. On the tenth day the total length was still 1 mm. greater than at first, but the nose-anus length had lessened by 24 per cent from shortening of the anal canal and the volume had decreased by 44 per cent. The hind legs were now 8 mm. long.

On the seventeenth day the total length had decreased to 40 mm. and the body length to 15 mm. The hind limbs were 13 mm. long and the left foreleg had broken through the skin. The volume was not measured, but was seen to be less than before. The shape of the head and body and the pigmentation were definitely those of a frog, and the mouth and jaws also had metamorphosed. The skin had become toughened to such extent that the right foreleg could not break through it, and on the next day a small incision was made in the skin to release this leg.

On the twentieth day the animal, a frog to all intents and purposes except for a narrow tail of 30 mm., was found dead. It was somewhat swollen, so the volume could not be taken, but the animal had decreased in size more than the average normal larva during metamorphosis.

Autopsy showed that the viscera were nearly completely metamorphosed, as in animal A. The kidneys and liver were especially small. The ovaries were large and the brain well differentiated. The other viscera also were those of a normal young frog.

D. (Pl. V. and table.)

This larva received 13 doses of pituitary substance, and reacted about the same as did larva C., but somewhat more rapidly, and in seven days its metamorphosis was further advanced than that of the other. Its volume by this time had been reduced by a third, its nose-anus length by a fourth, and its hind legs had lengthened to 5 mm.

By the twelfth day the total length and volume were rapidly decreasing, the hind legs were 13 mm. long and one foreleg had appeared. As in animal C, the other foreleg had to be liberated by operation because the skin had toughened, and like animal C, this animal was found dead in the aquarium two days later.

At autopsy its viscera were seen to have metamorphosed to the same extent as in animal C, except that the gastro-intestinal tract was not quite so completely differentiated, and the gills were somewhat further reduced in size.

E. (Pl. V and table.)

This larva received 21 one-half tablet doses and reacted as did D. In nine days it lost 45 per cent of its volume, its tail decreased in size and its head and body began to resemble those of a frog. In twelve days one foreleg broke through the skin and a few days later the other appeared. By the seventeenth day, except for a narrow tail the animal appeared quite like a frog. By the twenty-second day the volume was down to 40 per cent of the original, the hind limbs were 12 mm. long, the tail was still present but was becoming smaller and the body was fully reduced to the size, shape and color of a frog. The thin ventral and dorsal fins of the tail had nearly disappeared, giving this appendage a near-rod shape.

Autopsy showed a completely metamorphosed gastro-intestinal tract, including a very small liver and very large gall-bladder. There were small gills, large air-containing lungs, small kidneys, large spleen, spherical and well differentiated testes and a well differentiated brain.

F. (Pl. V, VI and table.)

This animal received 15 half-tablet daily doses, and it reacted very rapidly to the medication. There was at first an increase of 2 mm. in the length of the tail, but a decrease in the volume of the body. In five days the volume decreased from 0.93 cc. to 0.80 cc., the legs grew from 2 to 7 mm., and the anal canal shortened 2 mm. The body during this time had become slender from discharge of fecal contents and from contraction and shortening of the gut. By ten days these changes had gone on still further, and the animal had the general shape and color of a frog.

By the fifteenth day one foreleg had appeared, but the tough skin seemed to have prevented the appearance of the other. Except for this, and the presence of the tail, the animal resembled a fully formed frog. The tail had begun to shorten and its dorsal and ventral fins had almost completely disappeared. The volume of the animal had decreased to 60 per cent of the original, and the hind limbs had lengthened to 18 mm.

At autopsy were found a practically differentiated gastro-intestinal tract, gills that had decreased somewhat in size, lungs that were very large and full of air, small heart and kidneys, spleen and ovaries well developed, and brain fully metamorphosed.

G. (Pl. V and table.)

This large thyreoidless larva was kept in this group of animals to serve as a control and was fed algae and milk sugar, although such procedure was not really necessary since Allen, Hoskins and others have shown that thyreoidless larvae retain the larval condition under normal circumstances, and as shown in section I of this paper, milk sugar alone has no direct effect upon metamorphosis. This animal (G) was kept for 15 days in a dilute sugar solution and fed on algae. It continued to grow, but showed no signs whatever of metamorphosis. Its growth was somewhat more rapid than that of average thyreoidless larvae of the same age kept on a normal diet, but was little if any more rapid than the maximum growth of such larvae.

At the end of the experiment this animal had increased in total length from 47 to 52 mm., including an increase in body length of 3 mm. The volume had changed from 0.98 to 1.40 cc., a growth of 43 per cent as contrasted with a decrease in volume of 30 to 60 per cent suffered by the other larvae. This animal was thus from two to three times as large as the larvae that had received 15 doses of pituitary substance.

Autopsy showed its viscera all in the larval condition as previously described for thyreoidless larvae (see Hoskins and Hoskins '19b). The brain was especially small and undifferentiated, whereas the ovaries, which are not retarded by thyreoidectomy, were well developed and contained oöcytes visible on the surface of the gonad.

H. (Pl. V and table.)

This animal received 9 daily 1 grain doses of the anterior pituitary substance, and reacted about the same as the other thyreoidless larvae after the same amount of medication. The length decreased slightly, the anal canal disappeared, the volume decreased about a third and the hind legs grew to 10 mm. The animal was then killed, fixed and autopsied. The forelegs under the operculum were 4 mm. long. The shape of the body and the pigmentation of the skin were changing to those of a frog. The mouth had just begun to change. The stomach was being formed, the gut was shortened to about half the larval length, the liver was still large, but had formed its three lobes and was decreasing in size, having freed itself from the coil of gut formerly embedded within it. The gall-bladder had enlarged. The gills were still large, but the lungs were fully expanded and air-containing and the kidneys had decreased in size. The testes were spherical and well developed, and the brain was about half way between that of a larva and a frog.

I. (Pl. V, VI and table.)

This larva also received nine doses of the preparation and reacted about the same as did H, except that its loss in volume (55 per cent) was greater, and its tail became relatively smaller. Its leg growth was relatively the same as that of H.

At autopsy its liver, stomach, kidneys, lungs and spleen were found to be completely metamorphosed. The intestine was about three-fourths reduced to the frog type, the gills were slightly reduced, and the brain had become nearly differentiated.

J. (Pl. V, VI and table.)

This animal was treated similarly to I and reacted in the same manner, except that its loss in volume (35 per cent) was not so great.

The viscera were in practically the same condition as those of I.

DISCUSSION OF EXPERIMENTS OF SECTION II

In the above experiments it was noted that in most cases the length of the animal increased slightly during the first day or two of the hypophysis feeding, before involution began. In one case (AA) this added length persisted for ten days, although in this, as in other cases, the volume of the tail was steadily decreasing regardless of length, because of a shrinkage both dorso-ventrally and laterally. In this involution the tail did not react quite the same as it does in natural metamorphosis, the muscles and cartilage being more resistant than the skin and connective tissue.

The volume began to decrease in every case within twenty-four hours, and in all but one experiment, the decrease was continuous. A considerable portion of this loss in the first few days was due to discharge of feces, as occurs naturally with the shrinkage of the gut. The total loss in volume suffered by the larvae was quite as extensive as occurs naturally, being 63 per cent in one case.

One animal (AA) continued to metamorphose for thirteen days after the medication was stopped, indicating either that the absorbed pituitary substance persisted for some time in the larva or else that it had started some process within the animal that was able to continue after the intake of pituitary ceased. In all of the cases in which the jaws of the larvae began metamorphosis (AA, A, C, D, E, F) the animals quit eating the pituitary substance and could have been influenced after that time only by the extract soluble in the water of the aquarium or else by a persisting effect of the substance eaten previously. The animals' ceasing to eat the tablets may account for the failure of their tails to disappear entirely.

The effect of the medication on the viscera was evident earlier than the effect on the somatic structures so far as macroscopic changes could be noted. There occurred on the first day the decrease in the size of the abdomen referred to above and the anal canal began to disappear usually within three or four days, being entirely gone, in some cases, in five days.

At autopsy the viscera were found, in every case, to be further advanced in metamorphosis than were the somatic parts as a whole, although the skeletal development was well advanced. The gastro-intestinal tract differentiated fairly early, being nearly half completed in nine days. The shrinkage of the liver that occurs normally during metamorphosis was very marked in these experiments, in one animal (E) becoming actually smaller than the gall-bladder. The gonads which are not directly affected by metamorphosis resembled those already described for thyreoidless larvae. The kidneys and spleen underwent their usual metamorphic changes in most of the animals of these experiments, but the gills tended to persist for a longer time than they do in normal metamorphosis. The lungs are not affected directly either by thyreoidectomy or natural metamorphosis, as we have shown in a previous publication, and there was no effect on them in these experiments. In all cases they were noted at autopsy to be expanded and to contain air, but this is true also of the lungs of undifferentiated larvae. The brain, which in thyreoidless larvae develops much more slowly than normally, was markedly stimulated in its growth by the hypophysis feeding, and after but nine doses given to animal I, for example, the brain had changed almost completely to the shape found in young frogs.

The skeleton, as indicated by the growth of the legs, showed considerable variability in its response to the pituitary substance. Animal F (Pl. V) developed a larger skeleton in a shorter time than did E, although at the beginning of the experiment it was the smaller of the two animals. The skin developed in some cases more rapidly than did the legs, and in C, D and F the right foreleg was unable to break through it.

The action of the pituitary substance in these experiments was somewhat less extensive and less rapid than has previously been described for the thyreoid in experiments of the same kind.

GENERAL DISCUSSION

It has been believed for many years that the thyreoid and hypophysis are able, to a certain extent at least, to function vicariously. This idea was expressed by Rogowitsch '89, who noted hypertrophy of the hypophysis in rabbits, following thyreoidectomy, an experiment probably first performed by Raynard '34 and repeated since by a very large number of other investigators. In cases of pregnancy (Paton '13) and in naturally occurring myxoedema, there has also been noted pituitary hypertrophy (Boyce and Beadles '93). Ascoli '12 has shown, on the other hand, that after removal of the hypophysis of mammals the thyreoid tends to atrophy, and Adler '14 and others have verified this finding in the amphibia. In addition to the above mentioned effects of removing either the hypophysis or the thyreoid, many other changes have been described for other organs and tissues, and changes in either the thyreoid or hypophysis can be produced by experiments other than removal of one of them. Livingston '14, for example, noted hypertrophy of the pituitary after the spaying of rabbits. Jackson '17 found that the hypophysis of rats decreases in size during inanition; Cushing and Goetsch '15 described a similar decrease in the pituitary of woodchucks during hibernation; in both cases the hypophysis returned to normal when the animals were given a normal diet.

The effect on the hypophysis of thyreoidectomy in mammals has been seen since the experiments of Rogowitsch '89, by Hofmeister '94 and more recently by various workers (see Vincent '12, Biedl '13, or Paton '13). Viguier '11 obtained the same effect in lizards, and Hoskins and Hoskins '18, Rogers '18 and Larson '19 have noted it in amphibia. Hence the relationship between the thyreoid and the hypophysis indicated by this kind of experiments probably obtains in all classes of animals.

Response to feeding thyreoid substance has been investigated in many kinds of animals and with fairly uniform results. When large doses are administered the animals are poisoned, but when properly regulated amounts are used there occurs a stimulation which, however, has been interpreted differently by different investigators. This effect in mammals has recently been discussed by Hoskins '16, Herring '17, and Kojima '17, and in protozoa by Shumway '17. The classic studies of Gudernatsch '12, '14, have shown the remarkable stimulating effect of thyreoid extract when fed to amphibian larvae. Morse '14 found the action to be due to the iodine content of the thyreoid. He was unable to obtain it with inorganic iodine, but did obtain it with iodized blood albumen. Lenhart '15 stated that the effect on frog larvae was proportional to the iodine content of the thyreoid substance used, but he also was unable to get the same results with inorganic iodine. Lenhart pointed out further that the effect in hastening metamorphosis was of a general nature and not due to any specific differentiating property of the thyreoid. Romeis '15 using Lugol's solution likewise was unable to bring about precocious metamorphosis of frog larvae by administering inorganic iodine. Abderhalden '15 showed that the result could be obtained with thyreoid substance thoroughly digested and later, Swingle '18, repeating the experiments with iodine, was able to stimulate metamorphosis in normal frog and toad larvae and in those which had had their thyreoids removed. He hastened metamorphosis in frog larvae with M/1,100,000 iodine solution ('19). Allen '19 produced the same kind of stimulation in amphibian larvae which had had both the thyreoid and hypophysis extirpated.

From the above experiments, and especially from the work of Kendall '19, it seems highly probable that the active principle in the thyreoid is some iodine compound, and, as far as amphibia are concerned, inorganic iodine appears to be as capable of markedly stimulating metabolism as thyreoid substance itself. There are possibly various other organic and inorganic substances able to produce the same effect, if, as Kendall points out, it is simply in the nature of catalysis.

Experiments with the hypophysis are by no means so uniform in their results as are those with the thyreoid. There is an admitted relation of the hypophysis to carbohydrate metabolism as discussed recently by Keeton and Becht '19, and to skeletal and other growth (Cushing '12), but the exact details of these relationships are still in dispute. In higher animals, removal of the hypophysis (Cushing '12) is incompatable with life, although larval frogs are able to live without it (Adler '14, Smith '16 and Allen '16, Hoskins and Hoskins '19a), and Houssay '17 was able to keep alive some adult frogs from which the hypophysis had been removed.

From 1897 to 1916 there was about an even division of opinion as to whether pituitary feeding would or would not give positive results (for discussion see Schiff '97, Biedl '13, and Hoskins '16), but since then most of the papers published on the subject agree that at least with the feeding of the anterior lobe of the hypophysis, a definite stimulation of growth can be produced. This has been claimed for protozoa (Flather '19), worms (Wulzen '16), birds (Winternitz '16, opposed by Pearl '16) and mammals (Robertson '17 and Marinus '19). Numerous other papers on the subject will be found abstracted in the files of Endocrinology, 1917-20.

Massay '08 tried to prevent the usual symptoms following thyreoidectomy of dogs, by hypophysis-extract injections, and obtained negative results. Larson '19 with somewhat similar experiments reports that these symptoms can be prevented from occurring in thyreoidectomized rats by hypophysis feeding, but Allen '19a, states that he obtained negative results when he administered beef pituitary substance to thyreoidectomized tadpoles. As described above, anterior pituitary substance will bring about almost if not complete metamorphosis of thyreoidless frog larvae.

As to the effect of feeding hypophysis substance to normal tadpoles, Gudernatsch '12, '14, reported negative results with hypophysis extract carried from New York to Vienna and kept in the laboratory at room temperature. Abderhalden '15 performed a few experiments with an extract of thoroughly digested hypophysis substance and found it very toxic to his tadpoles, but noted that in a few cases it seemed to stimulate their development. He regarded his results as indefinite. Smith '18, states that anterior pituitary substance stimulates growth of frog larvae just before metamorphosis and then hastens this process.

That we were able to bring about early metamorphosis in normal frog larvae by the administration of anterior pituitary substance is not surprising, in view of the fact that hypophysis substance has previously been shown to stimulate metabolism and the fact that such stimulation is sufficient in itself to hasten metamorphosis of amphibians. As Lenhart '15 pointed out, in the numerous experiments wherein early metamorphosis of tadpoles has been induced, what really occurs is simply the hastening of a natural process. Nothing fundamental takes place during this hastened change of form that does not happen naturally at a lesser rate.

Concerning the manner of action of pituitary substance fed to animals, we have no certain explanation. We cannot as yet determine whether the action upon the metabolism is direct or whether the substance acts by stimulating some gland or other structures of the body. It is doubtful whether the influence of the hypophysis fed to normal tadpoles is exerted entirely upon the thyreoid because, as we described above, the same sort of phenomenon is seen when this substance is administered to larvae which have been deprived of their thyreoids. Moreover, the action is not simply a stimulation of all general metabolic processes, because thyreoidless larvae will live for months or years on a normal diet without undergoing metamorphosis, whereas they begin to metamorphose within twenty-four hours if anterior pituitary substance is administered to them. The hypophysis of these thyreoidless larvae has undergone a distinct hyperplasia, apparently in an attempt to make up the deficiency of thyreoid secretion, but it is not successful, and in these experiments the pituitary preparation may act through the animal's own hypophysis. Smith '18 was unable to cause metamorphosis of hypophysectomized larvae by hypophysis feeding, but as Allen '19b shows, larval amphibia which have been deprived of both thyreoids and hypophysis go nearly, if not completely, through metamorphosis if inorganic iodine is administered to them. But it is also true that the normal larvae in our experiments reacted more completely to pituitary feeding than did those which were without thyreoids, and more completely than did Allen's larvae which were without both thyreoids and hypophysis, react to iodine. Hence it seems probable that when the thyreoids and hypophysis are present their activity during metamorphosis is augmented by the administration of thyreoid, iodine, or pituitary, and in the absence of one or both of these glands, the above mentioned substances are able to supplement their activity to a considerable extent. It is quite possible that Allen's larvae and our thyreoidless larvae failed to metamorphose completely because of the fact that when their jaws metamorphose they cease eating the administered substances. Swingle '19, however, caused normal and thyreoidless larvae to metamorphose by placing them in a dilute solution of iodine, so it is probable that this halogen is absorbed in quantities sufficient to produce the effect noted. It has long been known that the skin of amphibia is pervious to substances soluble in water.

In the metamorphic processes produced in thyreoidless larvae by pituitary feeding, there was some variability of the minute details of these phenomena as described above. In some larvae the skeletal growth was relatively more rapid than in others, and the changes occurring in the different viscera were variable, the entire process not being quite so well co-ordinated as in normal metamorphosis.

Finally, as stated in the introduction, the results obtained by feeding preparations of dead ductless glandular substances to animals may be pharmacological rather than physiological, and may not represent the normal functions of the animal. This is certainly true of feeding inorganic substances such as iodine.

SUMMARY AND CONCLUSIONS

We have found that a preparation of the anterior lobe of beef hypophysis, which contains some form of iodine, 1:200,000 of fresh substance, when administered to normal frog larvae will bring about a precocious metamorphosis, resulting in the production of frogs the size of which varies with the size of the larvae at the beginning of the experiment. If the original larvae are very small, they never become as large as the controls and the resulting frogs are small. Such frogs have little vitality. If permitted to remain exposed to the air they die and dry down almost flat, losing their shape, and there remains but a very small percentage of the original volume. We have not yet studied these small frogs microscopically, but they appear to have a relatively high water content. Pituitary substance is more toxic to small than to larger larvae.

When the pituitary preparation was administered to thyreoidless larvae which would otherwise have remained in the larval form more or less indefinitely, a beginning of metamorphosis occurred within twenty-four hours; it progressed somewhat more slowly than in the other experiments just mentioned; but it ultimately became nearly complete by the time the animals were either killed or died spontaneously.

From these experiments the hypophysis, in its relation to amphibian metamorphosis, is to be ranked with the thyreoid as shown by the well known work of Gudernatsch.

We regard the results obtained as due to a stimulation of natural general metabolic processes, either directly or indirectly, but the exact nature of this action is not known. The effect is both progressive, as seen especially in the skeletal and cutaneous development, and retrogressive, as seen especially in the digestive tract and tail.

It is very doubtful that the action of the anterior pituitary substance is due merely to its iodine content, although such may be the case. Other tissues with traces of iodine will not produce the same effect as the pituitary.

It is quite possible that the initial stimulation in hypophysis feeding is exerted upon the calcium and phosphorus metabolism as is indicated by skeletal changes in these experiments, although intestinal transformation also begins very early.

The hypophysis and the thyreoid are closely related physiologically and can to some extent function vicariously.

Recent investigations by various workers with amphibian larvae have developed the following facts concerning the thyreoid and hypophysis:

1. Removal of the thyreoid hastens growth, causes hyperplasia of the hypophysis and prevents metamorphosis.
2. Removal of the hypophysis retards growth, retards development of the thyreoid, prevents metamorphosis, and retards development of cutaneous pigment.
3. Feeding thyreoid or hypophysis (or iodine) to normal larvae hastens metamorphosis.
4. Feeding thyreoid or hypophysis (or iodine) to thyreoidectomised larvae brings about metamorphosis.

5. Feeding hypophysis to hypophysectomised larvae stimulates growth but does not cause metamorphosis.

6. Feeding iodine to larvae with both the thyreoid and hypophysis removed causes metamorphosis.

LITERATURE CITED

Abderhalden, E.: Studien ueber die von einzelnen Organen hervorgebrachten. Substanzen mit specifischer Wirkung. I. Mitteilung. Verbindung die einen Einfluss auf die Entwickelung und den zustand bestimmter Gewebe ausüben. Arch. f. d. ges. Physiol. (Bonn), 1915, **162**, 99.

Adler, L.: Metamorphosestudien an Betrachierlarven. I. Exstirpation endocraner Drüsen. A. Exstirpation der Hypophyse. Arch. f. Entw. d. Org. 1914, **39**.

Allen, B. M.: The results of thyroid removal in the larvae of Rana pipiens. Jour. Exp. Zool. (Phila.), 1918, **24**.

— — — — Miscellaneous notes regarding experimental studies upon the endocrine gland of Rana and Bufo. (Abstract) Anat. Rec. (Phila.), 1919, **15**, 353.

— — — — The relation of the pituitary and thyroid glands of Bufo and Rana to iodine and metamorphosis. Biol. Bull. (Woods Hole), 1919b, **34**, 405.

Ascoli, G.: Die Folgen der Exstirpation der Hypophyse. Münch. med. Wchnschr., 1912, **59**, 519.

Gauman, E.: Uber das Thyrojodin. Münch. med. Wchnschr., 1896, **43**, 309.

Biedl, A.: Innere Secretion. Ihre physiologischen Grundlagen und ihre Bedeutung fur die Pathologie. Berlin, 1913.

Boyce and Beadles, '93. (Cited by Vincent, 1912.)

Cushing, H.: The pituitary body and its disorders. Philadelphia, 1912.

Cushing, H., and Goetsch, E.: Hibernation and the pituitary body. Jour. Exp. Med. (Phila.), 1915, **22**.

Denis, W.: A note regarding the presence of iodine in the human pituitary body. Jour. Biol. Chem., 1911, **9**, 365.

Flather, M.: The effects of some glandular extracts upon the contractile vacuoles of Paramecium caudatum. Biol. Bull. (Woods Hole), 1919, **37**.

Gudernatsch, J. F.: Feeding experiments on tadpoles. I. Arch. f. Entwick. 1912, **35**, 437.

— — — — —. Feeding experiments on tadpoles II. Further contribution to the knowledge of organs with internal secretions. Am. J. Anat. (Phila.), 1914, **15**, 431.

Hahn, A.: Einige Beobachtungen an Reisenlarven von Rana esculenta. Arch. f. Mik. Anat. 1912, **80**, 1.

Herring, P. T.: The action of thyroid upon the growth of the body and organs of the white rat. Quart. J. Exp. Physiol. (Lond.), 1917, **11**, 231.

Hoffmeister, F.: Experimentelle Untersuchungen über die Folgen des Schilddrüssen Verlustes. Beit. z. klin. Chir. 1894, **11**, 441.

Hoskins, E. R.: The growth of the body and organs of the albino rat as affected by feeding various ductless glands (thyroid, thymus, hypophysis and pineal). Jour. Exp. Zool. (Phila.), 1916, **21**, 295.

Hoskins, E. R., and Hoskins, M. M.: Further experiments with thyroidectomy in amphibia. Proc. Soc. Exp. Biol. and Med. (N. Y.), 1918, **15**, 102.

——————— (Abstract). Experiments with the thyroid, hypophysis and pineal glands of Rana sylvatica. Anat. Rec. (Phila.), 1919a, **16**, 151.

——————— The growth and development of amphibia as affected by thyroidectomy. Jour. Exp. Zool. (Phila.), 1919b, **29**, 1.

Houssay, B. A.: Recherches experimentales sur l'hypophyse de la Grenouille. Jour. de Phys. et Path. Gen. (Paris), 1917, **17**, 106.

Jackson, C. M.: The effects of inanition and refeeding upon the growth and structure of the hypophysis in the albino rat. Am. J. Anat. (Phila.), 1917, **21**, 321.

Keeton, R. W., and Becht, F. C.: The relation of the hypophysis to glycogenolysis. Am. J. Physiol. (Balt.), 1919, **49**, 248.

Kendall, E. C.: The physiologic action of thyroxin. Endocrin., 1919, **3**, 156.

Kojima, M.: Studies on endocrine glands. Quart. J. Exp. Physiol. (Lond.), 1917, **51**, 319.

Larson, J. A.: On the functional correlation of the hypophysis and the thyroid. Am. J. Physiol. (Balt.), 1919, **49**, 55.

Larson, M. E.: Effect of the extirpation of the thyroid gland upon the pituitary gland in Bufo. (Abstract). Anat. Rec. (Phila.), 1919, **15**, 353.

Lenhart, C. H.: Influence upon tadpoles of feeding desiccated thyroid gland in variable amounts and of variable iodine content. J. Exp. Med. (N. Y.), 1915, **22**, 739.

Livingston, A. E.: Effect of castration on the weight of the pituitary in rabbits. Proc. Soc. Exp. Biol. and Med. (N. Y.), 1914, **11**.

MacArthur, C. G.: A method of tissue analysis applied to the posterior and anterior lobes of cattle pituitaries. J. Am. Chem. Soc. 1919, **41**, 1225.

Marinus, C. J.: The effect of feeding pars tuberalis and pars anterior propria of the bovine pituitary glands upon the early development of the white rat. Am. J. Physiol. (Balt.), 1919, **49**, 238.

Masay, F.: L'Hypophyse. These, Bruxelles, 1908. (Cited by Vincent, 1912.)

Morse, M.: The effective principle in the thyroid, accelerating involution in frog larvae. J. Biol. Chem., 1914, **19**, 421.

Paton, D. N.: Regulators of Metabolism. London. 1913.

Pearl, R.: Reproduction in the fowl. IV. On the effects of feeding pituitary body (anterior lobe) substance and corpus luteum substance to growing chicks. Proc. Nat. Acad. Sc. (Wash.), 1916, **2**, 50.

Raynard, C. R.: C. R. des traveaux de l'ecole royale veterinaire de Lyon pendant l'annee scholaire. Rec. de Med. Vet. Prat., 1836, **13**, 8. (Cited by Vincent, 1912.)

Robertson, T. B., and Delprat, M.: Experimental studies on growth. IV. The influence of tethelin upon the early growth of the white mouse. J. Biol. Chem., 1917, **31**, 567.

Rogers, J. B.: The effect of the extirpation of the thyroid upon the thymus and pituitary glands of Rana pipiens. J. Exp. Zool. (Phila.), 1918, **24**.

Rogowitsch, N.: Die Veränderungen der Hypophyse nach Entfernung des Schilddrüse. Beitr. z. path. Anat., 1889, **4**, 453.

Romeis, B.: Experimentelle Untersuchungen ueber Wirkung innerersekretorische Organe. II. Der Einfluss von Thyroidea und Thymus Fütterung auf das Wachstum die Entwickelung und die Regeneration von Anurenlarven. Arch. f. Entwickelungsmech, 1915, **41**.

Shumway, W.: Effects of thyroid on Paramecia. J. Exp. Zool. (Phila.). 1917, **22**, 529.

Simpson, S., and Hunter, A.: The relations between the thyroid and pituitary glands. Proc. Soc. Exp. Biol. and Med. (N. Y.), 1909, **7**, 11.

Schiff, A.: Beeinflussung der Stoffwechsels durch Hypophysis—und Thyreoidtherapie. Wiener klin. Wchnschr., 1897, **10**, 277.

Smith, P. E.: The effects of hypophysectomy in the early embryo upon the growth and development of the frog. Anat. Rec. (Phila.), 1916, **11**, 57.

——————The growth of normal and hypophysectomised tadpoles as influenced by endocrine diets. Univ. California Pubs. (Physiol. Ser.), 1918, **5**, 11.

Schnitzler, J.: Ueber das Vorkommen des Thyreojodins im menchlichen Körpers. I. Thyreojodin im der Hypophyse. Wiener klin. Wchnschr., 1896, **9**, 657.

Swingle, W. W.: Iodine as the active principle of the thyroid gland. Endocrin., 1918, **2**, 283.

———————Iodine and the Thyroid. III. The specific action of iodine in accelerating amphibian metamorphosis. J. Gen. Physiol. (N. Y.), 1919, **1**, 593.

Viguier, G.: Modifications de l'hypophyse aprés thyroidectomie ches un lezàrd (Uromastrix acanthinurus, Bell). C. R. Soc. Biol. (Paris), 1911, **70**, 222.

Vincent, S.: Internal secretion and the ductless glands. London. 1912.

Wells, H. G.: The physiology and therapeutics of the thyroid gland and its congeners. J. Am. M. Assn. (Chgo.), 1897, **29**, 1007.

Winternitz, M. C.: Some observations on the effects of feeding glands of internal secretion to chicks. Johns Hopkins Hosp. Rep. (Balt.), 1916, **18**, 21.

Wulzen, R.: Effect of hypophysis feeding on the growth and fission of planarian worms. J. Biol. Chem., 1916, **25**, 625.

PLATES I to VI
TABLE

PLATE I.

Fig. 1. Hypophysis-fed tadpole. (Ex. 1) 15 days after beginning of experiment. Body 11 mm. Total 32 mm. X 2.

Fig. 2. Normal tadpole. Body 13.5 mm. Total 32 mm. X 2. Both drawn from the living animal.

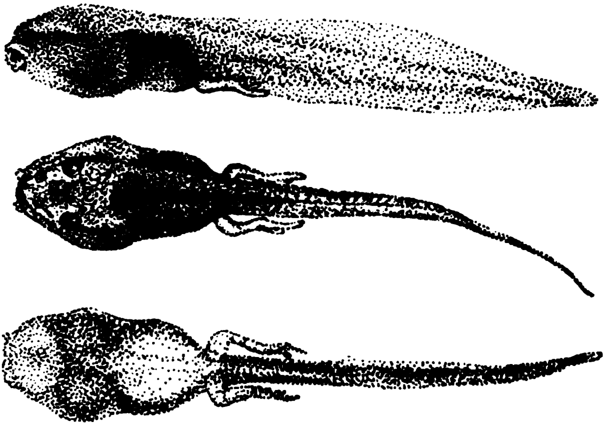


Fig. 1

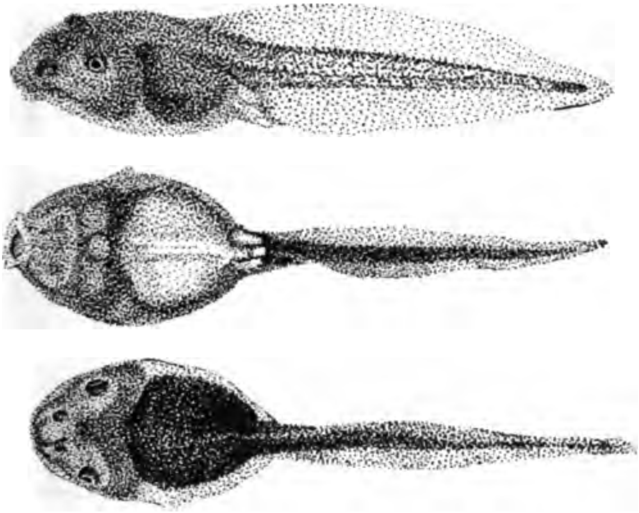


Fig. 2

PLATE II.

Fig. 3. Hypophysis-fed frog. (Ex. 1.) 28 days after beginning of experiment. Body 8.8 mm. X 2. Drawn from the living animal.

Fig. 4. Normal frog. Body (fixed) 10.4 mm. X 2.

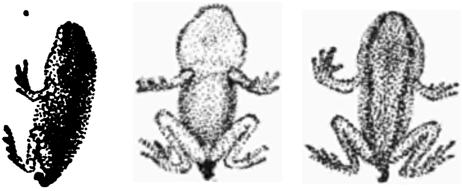


Fig 3

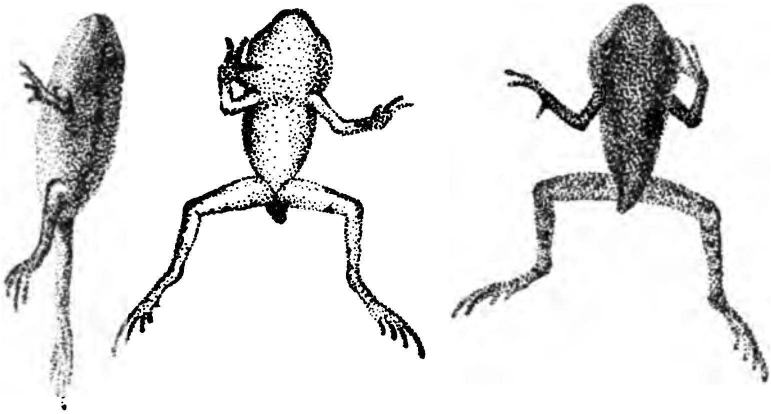


Fig 4

PLATE III. All drawn X 2 from the living animals.

Fig. 5. Hypophysis-fed tadpole (2 A) 18 days after beginning of experiment. Body 9.5 mm. Total 21 mm.

Fig. 6. Normal tadpole. Same age as above. Body 12 mm. Total 28 mm.

Fig. 7. Hypophysis-fed tadpole (Ex. 2 A) 28 days after beginning of experiment. Body 8 mm. Total 21.5 mm.

Fig. 8. Hypophysis-fed tadpole (Ex. 2 B) 13 days after beginning of experiment. Body 12 mm. Total 28 mm. Compare with Fig. 6 for tadpole of same length.

Fig. 9. Hypophysis-fed tadpole (Ex. 2 B) 31 days after beginning of experiment. Body 15 mm. Total 35 mm.

Fig. 10. Normal tadpole. Same age as in Fig. 9. Body 15 mm. Total 33 mm. (Later the controls became larger than the hypophysis-fed larvae.)

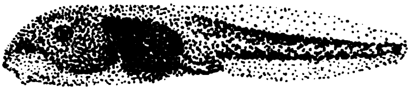


Fig. 5

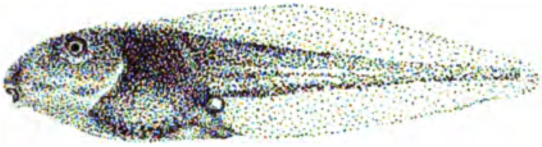


Fig. 6

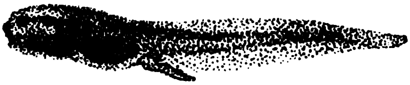


Fig. 7

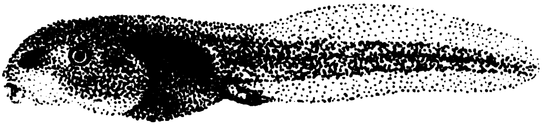


Fig. 8

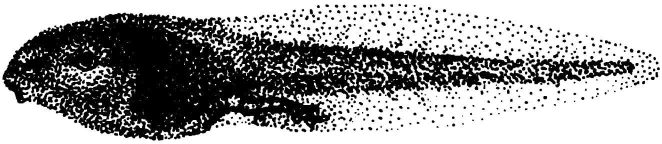


Fig. 9

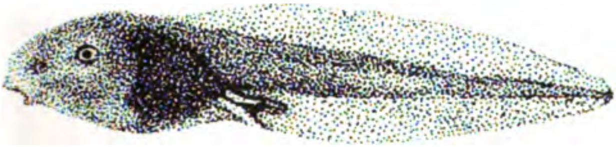


Fig. 10

PLATE IV.

Figures D to J. Normal Rana sylvatica natural size photographed in alcohol after fixation. The larvae (D to N) had reached their maximum size and were on the point of beginning a rapid metamorphosis when fixed. Note the shrinkage in size that has occurred during metamorphosis (B to J).

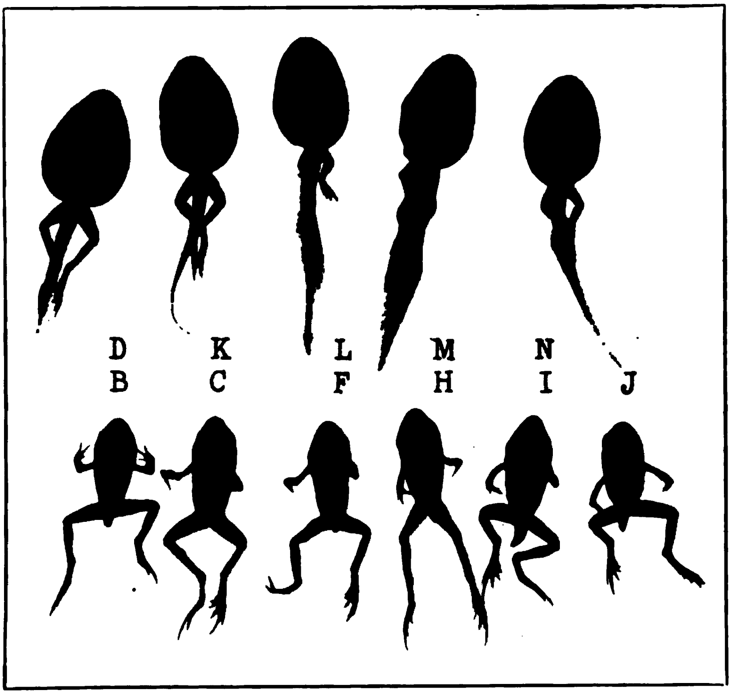
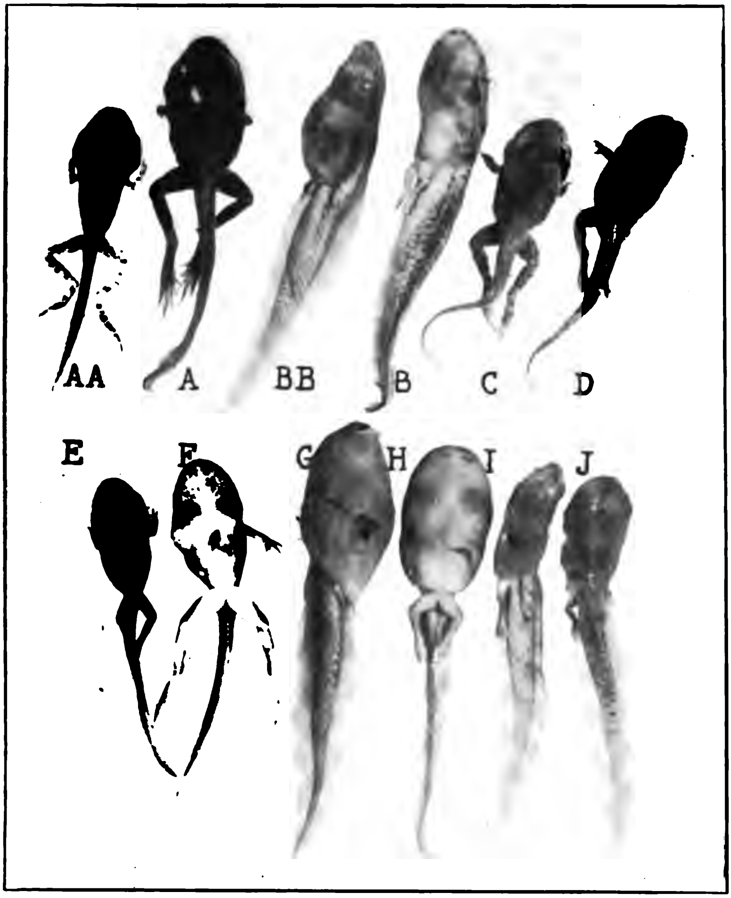

D
K
L
M
N
B
C
F
H
I
J

PLATE V.

Figures A.A. to J. Thyreoidless Rana sylvatica, natural size. Photographed in alcohol after fixation. For size and number of doses of anterior pituitary substance administered see Table. Note G. which received no medication. The development is roughly proportional to the amount of pituitary given, and the size of the frogs is proportional to the size of the larvae before medication. A, C, and D died in the aquaria and became slightly swollen.


AA
A
BB
B
C
D
E
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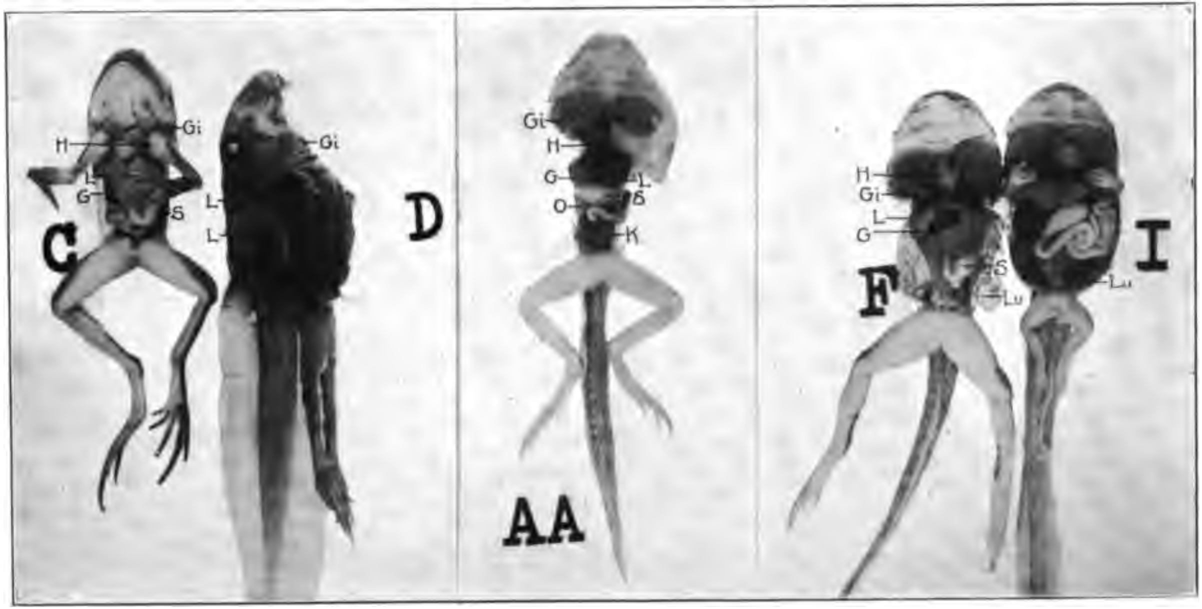
G
H
I
J

PLATE VI.

Thyreoidless and control larvae and "frogs" of Rana sylvatica treated with anterior pituitary substance. Same animals as in Plate V. but dissected. X 3. C and D—Controls; AA, F and I—Thyreoidless.

Abbreviations: G.—Gall-bladder, Gi.—Gill, H.—Heart, K.—Kidney, L.—Liver, Lu.—Lung, O.—Ovary, S.—Stomach.


C
Gi
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Lu
F
I
Lu

TABLE SHOWING THE EFFECT OF TREATING THYREOIDLESS LARVAE WITH ANTERIOR PITUITARY PREPARATION.

Beginning	2 days	4 days	9 days	10 days	12 days	15 days	22 days	31 days	Doses
mm. cc.	mm. cc.	mm. cc.	mm. cc.	mm. cc.	mm. cc.	mm. cc.	mm. cc.	mm. cc.	
A.A. 42-19.0-2.0-0.98	43.5-19.0-	45-19.0-0.75	45-16.0- 5-0.65	45-14- 5.5-0.65	41-14- 6-0.75	42-14- 9-0.75	40-15-16-0.50	36.5-15-17-0.35	*15
A. 50-20.0-2.0-1.50	41.0-20.0-2.5-1.20	41-20.0-3-1.10			48-17-15-0.96	44-17-20-**			18
B. 46-20.0-1.5-1.30	47.0-20.5-2.5-1.10	48-19.0-3-1.00	47-16.0- 7-0.85	**					8
B.B. 47-20.0-2.5-1.20	48.0-20.0-	45-18.5-3-0.80	*						3
C. 43-21.0-2.0-1.35	43.5-20.5-2.5-1.20	44-18.0-3-1.00		44-16- 8.0-0.75		40-15-13-**			18
D. 42-18.5-1.5-0.90			41-14.0- 5-0.60		39-14-13-**				13
E. 44-19.0-1.5-1.00			41-14.0- 5-0.55		38-14-11-		36-14-12-0.40	*	21
F. 45-19.0-2.0-0.93		47-17.0-7-0.80		45-16-13.-0.70		42-17-18-0.56	*		15
G. 47-19.0-2.0-0.98		48-21.0-2-1.06		51-21- 2.0-1.08		52-22- 3-1.40	*		0***
H. 53-23.0-2.5-1.45		54-20.0-5-1.22	50-19.0-10-1.05	**					9
I. 46-20.0-2.0-1.05		43-16.0-3-0.80	41-14.5- 7-0.50	*					9
J. 44-19.0-2.0-1.00		43-16.0-3-0.85	42-14.5- 7-0.65	*					9

N. B.—The first number, total length; the second, nose-anus length; the third, bind-leg length, all in mm.; and the fourth, volume, in cc.
*Killed. **Died. ***Control thyreoidless.

Pioneers in Embryology

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PIONEERS IN EMBRYOLOGY *

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MINNEAPOLIS

How living things are generated is a question of universal interest which has attracted attention since ancient and even prehistoric times. So far as we know, however, the Greek philosophers were the first to make a systematic study of embryology. Among these, Aristotle (B. C. 384-322) was preeminent. Like Hippocrates, his immediate predecessor, he was descended from a line of physicians, from whom he may have inherited a taste for science. Aristotle was a pupil of Plato, but differed from him fundamentally in his attitude toward philosophy. Plato was an idealist, who relied mainly on intuition, while Aristotle was a realist, and held that observation is the proper basis for knowledge. This view, now a commonplace of science, but then a novel idea, was emphasized by Aristotle thus: "One must believe the observation rather than the theory, and the latter only when it is in agreement with the facts observed."

THE WORK OF ARISTOTLE

Aristotle was a teacher of Alexander the Great, and had influence at court. In order to make an extensive study of animals, he obtained from his royal patron a grant of a large sum, 800 talents, or the equivalent of about $200,000. This is interesting as perhaps the first governmental subsidy for scientific investigation on a large scale. Aristotle used this amount in employing numerous research assistants who traveled over the known world (the regions encircling the Mediterranean), collecting specimens and gathering information from farmers, hunters, fishermen and all who knew anything about animals.

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* A lecture given under the auspices of the Graduate School, University of Minnesota.

Thus, Aristotle was able to collect a relatively large amount of data for study. In addition to original observations, he also compiled the views of his predecessors, and even at that time refers to the opinions of "the ancients." For while the period of some twenty-two centuries since Aristotle seems a long time, we must not forget that a much longer preceding period had been required to accumulate slowly the small stock of common knowledge then available. Through his own observations and efforts, Aristotle was able to extend greatly this knowledge, and to establish the science of biology.

His biologic work is embodied chiefly in three books: "History of Animals,"[1] "On the Parts" and "Generation of Animals."[2] The "History of Animals" is a classic which should be read by every student in biology and medicine. It contains in briefer form his views on embryology. They are elaborated more fully in the "Generation of Animals," which was the first systematic treatise on embryology. We shall refer briefly to some of his principal results in order to give an idea of the scope and character of Aristotle's work in embryology.

Some 500 species of animals (chiefly vertebrates) are mentioned by Aristotle, and his descriptions in many cases include observations on their mode of reproduction. He recognized among animals two fundamentally different methods of reproduction, which we now designate as biogenesis and abiogenesis. Abiogenesis, or spontaneous generation of living things from lifeless matter was a universal belief at that time, and was thought to occur, by the action of air and warmth on slime, etc., not only among the lower forms of life, but also among vertebrates, such as eels, frogs, and even small mammals. This view seemed to be proved beyond question by everyday experience and even by careful observations.

Aristotle mentions, for example, certain marshy ponds which dried up, and in which eels appeared when the ponds were again filled with water by the rains. Such evidence appeared to him conclusive proof of spontaneous generation, a doctrine that has persisted among the uneducated throughout all ages down to the present day. Even among scientists, abiogenesis was practically unquestioned before the time of Redi, in the seventeenth century, and only after 200 years more of controversy was it definitely disproved by the classical experiments of Pasteur. Even now, many biologists believe that abiogenesis of protoplasm is at least a theoretical possibility, which some day may be successfully accomplished by artificial means.

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[1] Aristotle: History of Animals, translated by Richard Cresswell, London, 1891.

[2] Aristotle: Generation of Animals, Von der Zeugung und Entwicklung der Thiere, translated by Aubert and Wimmer, Leipzig, 1860.

Aristotle recognized biogenesis, the reproduction of life from living beings, as the prevailing method. He also observed that in some species this might occur asexually (by budding or by parthenogenesis), although the sexual method is usual among the higher animals. The essential principle of the sexual method, the union of male and female elements to form a new organism, was of course already well known. Aristotle studied the process carefully in various species, and classified animals into the oviparous, or egg-producing, including most forms below mammals, and the viviparous, or live-producing mammals. He even noted an intermediate form ovoviviparous, in some elasmobranch fishes, an observation apparently not confirmed until the time of Johannes Müller, more than 2,000 years later.

Unfortunately, Aristotle classified the cocoons of the insect pupae as eggs, a mistake that later misled even Harvey, and give rise to much confusion. Aristotle recognized that the eggs, which are produced by the female, must be fertilized by the semen or sperm of the male, in order to be capable of further development. He studied with care the formation of the egg in the ovary of the hen, and also observed the process of the development of the chick day by day during incubation.

Some of his more important observations on the developing chick are as follows: After three days of incubation, during which he could see no definite change, the heart appears as a pulsating red spot, in the white of the egg near the yolk. From the heart extend two sets of vessels, one to the yolk and the other to the membranes. Soon the body of the chick embryo appears, the head, especially the brain and eyes, being relatively large, and the tail end of the body very small. The various organs, liver, lungs, etc., appear successively, by epigenesis, and not simultaneously. By the tenth day, all parts are distinct, the intestinal canal extending toward the navel. The yolk sac is gradually absorbed for nutriment. The brain matures slowly, and the roof of the skull is the last part of the skeleton to form.

In the viviparous animals (mammals) Aristotle described the process of reproduction as consisting in an intra-uterine intermingling of the male semen with the female semen. The latter is described as formed from the menstrual fluid in the human female and from a corresponding substance in the females of other mammals during the rutting season. Aristotle's ignorance of anatomy is evident from his view that in both sexes the semen is secreted by the walls of the sexual ducts or passages, the true significance of the testes and ovaries being unrecognized. The material substance with the "vegetative spirit" for the embryo was supposed to be derived from the female, corresponding to the egg of oviparous forms, while the developmental stimulus, or "generative spirit," was ascribed to the male semen. The embryo and the surrounding membranes are supposedly formed by a coagulation of the menstrual fluid, the process being compared to the action of rennet in curdling milk. The formation of the embryonic body and organs was found to be in general agreement with that of the chick, as outlined before. The same sequence was noted, the inner parts of the embryo appearing before the outer, and the upper part of the body before the lower. The "nobler" tissues (the flesh and sense organs), were supposed to develop from the "purest" portion of the nutriment, while the "inferior" structures (bones, tendons, nails, hair) come from the residue.

Aristotle also studied human embryos, including one at forty days, "about as large as a large ant." He speculates at length on many questions concerning human embryology, but is usually cautious in his conclusions, as for example in this passage:

> If the child is a male, a movement is usually felt on the right side of the groin, in about forty days; if a female, a movement occurs on the left side in about ninety days. We must not suppose, however, that an accurate judgment can be formed in this way, for it often happens that the movement is felt on the right side when a female child, and on the left side when a male child is conceived. All these and such like things vary in a greater or less degree.

Aristotle also observed and classified monstrosities. Rejecting various superstitions as to their origin, he established a rational teratology by explaining the various malformations as developmental defects. He also discusses at length the nature of heredity, opposing an earlier theory resembling the later "pangenesis" of Darwin. It is not possible, he says, that the semen could be derived from all parts of the body, each to reproduce its corresponding part, for then it would be impossible for a crippled man to beget a normal child.

Many other interesting observations and doctrines of Aristotle must be passed over, but the foregoing will illustrate the range and importance of his work. In spite of numerous errors and crudities that were inevitable in such pioneer work, he established biology on a scientific basis, and formulated many of the problems that have occupied attention down to the present day.

Although embryology was thus established on a good foundation, the conditions in the following period were unfavorable for its further development. The Grecian and Roman civilizations were overwhelmed by successive wars and final invasions by the barbarians. During the middle ages, the all-powerful church directed attention to theological matters, and the study of science was discouraged and neglected. In embryology, a few scattered observations on minor details were made from time to time (by Galen, Fabricius and others), but the teachings of Aristotle on this subject remained virtually unchanged and unchallenged for eighteen or nineteen centuries, down to the time of Harvey.

DISCOVERIES BY HARVEY

Even Harvey (1578-1657), the keen-minded discoverer of the circulation of the blood (1628), frankly adhered for the most part to the embryologic doctrines of Aristotle, to whom he refers respectfully as the "Prince of Philosophers." Nevertheless, Harvey's work "On Generation" (1651) is a very important contribution, based on many years of observation and study, especially on the development of the chick and the deer.

In the chick, Harvey followed the formation of the ovarian egg and the development of the chick during incubation. To the accounts of Aristotle and of Fabricius (Harvey's teacher), he added much of importance.

He correctly located the origin of the embryo in the whitish yolk-spot, or cicatricula. In the center of this area, he noted the pulsating heart at the close of the third day, but believed that the blood arose still earlier. He concludes that "the blood is the generative part, the fountain of life, the first to live, the last to die, and the primary seat of the soul." The various organs were found to arise successively by epigenesis, as noted by Aristotle, but are described more accurately and in greater detail.

In one respect Harvey differed from Aristotle, and in this case erroneously, by denying an actual contact of the male semen with the egg during fertilization. Harvey found it impossible to pass a probe or an injection of water up the female tract in either birds or mammals; and he therefore concluded that such a passage is likewise impossible for the male semen. He was thus driven to the assumption of a fertilizing action by the sperm at a distance, which he compared with the action of a contagion, or of a magnet on iron.

In the deer, Harvey had unusual opportunity to study the process of reproduction in the hunting parks of his royal patient, King Charles I. Harvey corrected Aristotle's view as to the source of the male semen, and traced it to the testis; but, like Aristotle, he failed to locate the origin of the mammalian ovum (which was later traced to the ovary by De Graaf). Harvey disproved the doctrine of a female semen, showing by careful dissections in the deer and other mammals that nothing of the kind is observed in the female either before or after copulation. He found the (mammalian) ovum first apparent in the uterus, being unable to trace any connection between the ovum and the ovary or the male spermatic fluid.

Thus, on account of the inherent difficulties of the subject, which baffled him despite his most careful observations, Harvey fell into serious errors. Even his greatest generalization, that all life comes from the ovum ("ex ovo omnia"), is imperfect in some respects. In mammals, by "ovum" he meant the intra-uterine sac, within which the embryo (as we now know) is already relatively advanced in development. And in lower forms of life (insects, etc.) he still admitted that the ovum may arise by putrefaction or by the spontaneous generation of Aristotle. He also had an erroneous idea concerning the nature of the metamorphosis of the insect in the "egg" (cocoon).

Yet Harvey's work was of great importance in the advancement of embryology. He was able to trace both the earlier and the later development of the higher animals in much greater detail than was hitherto known, not only in the chick and deer, but also in man. He discerned the principal features of development, month by month, in the human embryo and fetus. Most important of all, he led the way to a renewed study of embryology by direct observation and experiment, the only road by which the truth can finally be reached.

The work of Harvey, in which only a simple magnifying glass was used, practically terminates what may be called the premicroscopic period. The introduction of the compound microscope, even the very imperfect instrument of the seventeenth century, gave an indispensable means and a great stimulus to the further investigation of embryology.

PROGRESS MADE POSSIBLE BY THE MICROSCOPE

Malpighi (1628-1694), by the use of the microscope, was able to add many details of importance to the observed process of development. Although a better observer than Harvey, Malpighi nevertheless made one serious error. In the chick he found the embryo already formed in the unincubated egg (owing to the hot weather of the Italian summer), and hence he proclaimed the doctrine of preformation of the embryo, in opposition to the doctrine of epigenesis previously taught by Aristotle and Harvey, and hitherto universally accepted.

This doctrine of preformation (or "evolution," as it was then termed) was further supported by the observations of Malpighi (also of Swammerdam and others) which revealed an unsuspected complexity of structure in the insect "eggs" (cocoons) and larvae, hitherto believed to be virtually unorganized. Bonnet taught that the embryo preexists in the egg as an invisible network of minute tubes, through which the heart pumps blood, furnishing nutriment to fill up the meshes of the net during the process of development. Haller and others during the eighteenth century, inspired by the philosophy of Leibnitz, pushed the preformation theory to the extreme limit, holding that nothing is really formed anew; that the ovum contains in miniature not only the adult which will develop from the embryo, but also, concentrically encased, similar germs of all succeeding generations. Thus it was seriously calculated that the ovary of Eve must have included 200,000 million minute human beings!

Another amusing corollary of this theory, illustrating also the theological tendency of the time, was furnished by Vallisnieri.[3] He argued that the parasitic intestinal worms (whose life history was then unknown) must likewise have been preformed within the human body and handed down from the first man, Adam. It was thought, however, that they were probably harmless until after the sin of Adam; and that they might have been transmitted in the form of eggs through Adam's rib in the creation of Eve, thus reaching the female.

Another phase of the embryologic problem was initiated by the discovery of the spermatozoa, first seen under the microscope by a medical student, Hamm (Hamen), at Leyden about 1675. He pointed them out to his teacher, Leeuwenhoek, who described them and claimed that they, rather than the egg, represent the real source of the embryo. Then arose a spirited controversy between the "ovists" and the "animalculists." The ovists claimed that the spermatozoa are merely parasitic organisms of no genetic significance, while the animalculists urged that the spermatozoa represent the essential elements in reproduction, the egg merely furnishing a nest or nutriment. Spallanzani proved that the spermatozoa are indispensable, since filtered semen was found to be impotent.

Furthermore, since preformation (or predelineation) was the prevailing doctrine, some investigators (Dalenpatius, Hartsoeker and others) claimed to have observed a miniature adult ("homunculus") in the spermatozoon under the microscope, and figures were actually published of such, showing the head, arms and legs. The climax was reached by Andry,[3] whose fanciful descriptions included a small trap-door in the ovum, large enough to admit only one spermatozoon of the many swarming around and seeking entrance. Savage conflicts were said to occur among the contesting spermatozoa; and if the victor had been injured, by the loss of a limb, for example, the embryo would present

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3. Rádl, E.: Geschichte der biologischen Theorien seit dem Ende des siebzehnten Jahrhunderts, Leipzig, 1905-1909.

a similar defect, resulting in a congenital malformation!

A new era in embryology arose with the work of C. F. Wolff (1733-1794), who described the embryonic organs of the chick as arising from leaflike sheets, similar to those of embryonic plants. Wolff revived the epigenetic theory of Aristotle and Harvey, but his work was overshadowed by the prevailing preformation doctrines of the eighteenth century. Only later, in the early part of the nineteenth century, did his observations receive merited attention, when they were confirmed by Pander and especially by von Baer, by whom they were extended to form the modern germ-layer theory.

Von Baer (1792-1876), who discovered the mammalian ovum (1827), is generally considered the founder of modern embryology. The subsequent establishment of the cell theory and its application to embryology have largely revolutionized our ideas of the subject and have extended it in many ways, especially in its relation to heredity and to evolution. While these modern phases of embryology are not within the scope of the present paper, it may be noted that some of the older problems, notably the question of preformation versus epigenesis, still confront us, though in a somewhat different form. That the regions of the future organism are already determined while the embryo is still an apparently homogeneous disk was shown by His (1874), and has since been experimentally proved.

The earlier process of fertilization and segmentation has been worked out in great detail for various classes of animals, though not as yet in man. The sperm and ovum usually show no trace of preformation in the original sense of the term, although the polarity of the unfertilized egg in many cases appears to determine the axis of the future embryo. The time when definite organ-forming areas can be recognized varies in different species. The early development appears to be essentially epigenetic, probably consisting in a definite series of reactions between the fertilized ovum and its environment. But we know that the parental germ plasm, probably the chromosomes, must carry over *something* which predetermines the future organization. What this something may be, we do not yet know. Some biologists consider the problem insoluble. But others, encouraged by the increasing knowledge in the fundamental sciences of chemistry and physics, and by the recent rapid progress in the realm of experimental embryology, are hopeful that some day it may be possible to explain the riddle of embryology—how does the egg produce the organism?

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THE EFFECTS OF INANITION IN THE YOUNG UPON THE ULTIMATE SIZE OF THE BODY AND OF THE VARIOUS ORGANS IN THE ALBINO RAT

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FIVE CHARTS

The question as to the effects of malnutrition during infancy and youth upon the capacity for later growth is of especial interest at present, on account of the prevalence of famine in connection with the world war. It is generally believed that early starvation may result in permanently stunting the later growth of the body, although accurate data for the human species are lacking. The results of animal experiments on this subject are somewhat contradictory. Aron ('10, '11, '14) and Brüning ('14) found that severe underfeeding of young dogs and rats apparently prevents them from reaching normal adult size upon later full feeding. On the other hand, Hatai ('07) and Stewart ('16) obtained complete recovery upon refeeding rats which had been underfed for short periods beginning at three or four weeks of age. Osborne and Mendel ('14, '15) also found no suppression of growth capacity in young albino rats whose growth had been retarded for long periods by various inadequate diets. The object of the present investigation is to determine the ultimate effect of such underfeeding when begun earlier (in the new-born) or when prolonged over a very extensive period. The study is also extended to include the effects upon the final weights of the various component parts, systems, and organs of the body.

MATERIAL AND METHODS

The white or albino rat (Mus norvegicus albinus) was used in the experiments, for which it is in many respects well adapted. It is hardy and thrives in captivity. It breeds rapidly (period of gestation three weeks), reaches sexual maturity at ten weeks, and adult size within a year. The normal growth rate and variability of the albino rat and its various organs have also been very thoroughly worked out, chiefly by Donaldson, Hatai, Jackson, and Lowrey, and normal growth tables by Donaldson ('15) are available for comparison. Moreover, the effects of acute and chronic inanition upon the weight of the body and of the various organs in the rat at different periods have been studied by Jackson ('15, '15 a), Stewart ('16, '18, '19), and Jackson and Stewart ('18, '19). The data available from these studies make possible a comprehensive view of the effects of inanition at various ages and the rapidity of recovery upon refeeding in an organism whose normal growth rate and variability are well known. The lack of such data frequently makes it impossible to draw trustworthy conclusions from the results of experimental work, especially when the observations are limited in number.

In the present investigation, thirty-eight litters of albino rats from the colony in The Institute of Anatomy were used. About half of the rats died from starvation during the experiments and are excluded from consideration. One hundred and thirteen rats survived, including 35 male and 35 female test rats, with 27 male and 16 female normal controls. In general, test rats and controls were available from each litter, as shown by the data in table 1. In this table, the letters 'St' (Stewart) refer to the series to which the rat belonged, the number preceding the decimal point indicates the litter, and the number following designates the individual. The final letter 'm' indicates male, or 'f,' female.

As further shown in table 1, the experiments may be divided into (A) those in which the preliminary underfeeding began at birth, and (B) those beginning at three weeks of age. The rats in division A were underfed by removal from the nursing mother at successive intervals, as described by Stewart ('18). In eight litters, the test rats, which weighed about 5 grams at birth, were retarded so as to reach only about 10 or 12 grams (the normal being 20 to 25 grams) at three weeks of age. After this they were fully fed, as were the controls throughout. They received (after the weaning period) an abundant diet of whole wheat (Graham) bread soaked in whole milk. Water from the city supply (Mississippi River) was given ad libitum throughout. In one litter (no. 86) the underfeeding was similarly prolonged from birth to four weeks of age, in three litters to six weeks, and in nine litters to about ten weeks (the extreme for this group being eighty-three days). The underfed rats at ten weeks (beginning of refeeding) had reached only about 15 or 16 grams in body weight, the normal at that age being over 100 grams.

In division B, the underfeeding did not begin until the age of three weeks (the weaning period), at a body weight of 20 to 25 grams. In one litter (no. 33) the test rats were refed at twenty weeks (138 days), the body weights then being 33 to 43 grams. In the remaining sixteen litters, the underfeeding was prolonged to nearly a year of age, the average being 342 days (range 235 to 375 days). The body weights of the test rats at this time (beginning of refeeding) averaged about 60 grams, while the normal controls had reached their maximum adult size (about 200 grams in the females and 250 grams in the males).

The curves of the average body weights in the various test and control groups (sexes separately) are shown in charts 1 to 5. The composite curves were constructed from the average body weights for the individuals of each group at corresponding ages, excepting in the refed rats. Since the test rats in each group were not all refed beginning at the same age, the average date of the beginning of refeeding in each group was taken as the starting point for the refed animals, and their body weights arranged and averaged according to the number of days of refeeding in each case.

The rats were well cared for throughout the experiments, being kept during underfeeding in a warm room on account of unusual susceptibility to cold at this time. They were weighed daily at the beginning of the underfeeding and the refeeding periods, the time of weighing being later extended to intervals of several days. The males and females of the same litter were usually not separated, and the number of litters born to each female is recorded in table 1. While no care was taken to keep males with the females constantly in all cases (and hence the number of litters is not the maximum possible), it may be stated that the test rats had at least as good an opportunity for breeding as did the controls.

At the end of the experiments, the rats either died or were killed, as indicated in table 1. In forty-five cases (28 test rats and 17 controls) autopsies were performed, and the weights of the various parts, systems and organs recorded. The technique used was the same as described in the earlier papers by Jackson and Stewart. In this series, Stewart was responsible for the care of the animals and the performance of the autopsies.

The data for the organ weights (also body length and tail length) are given in table 2 under four groups: those refed after underfeeding from, 1) birth to 3 weeks; 2) birth to 10 weeks; 3) 3 weeks to 20 weeks of age, and, 4) 3 weeks to nearly a year (average 342 days) of age. The controls in each group are not all from the same litters as the test rats, some being added (selected from the other groups) to make the average body weight of the controls about equal to that of the corresponding test rats in each group. In the fourth group, however, controls were not available so low in body weight as the test rats, and a different mode of comparison was used. For the body parts and systems of this group data from Jackson and Lowrey ('12) were used for the normal in rats of corresponding body weight. For the individual organs, the control rats (four males, eight females) from the corresponding litters were used, although they were much heavier than the test rats. Following a method suggested by Donaldson ('15), both controls and test rats were compared with the Wistar norm for rats of the same body weight (rather than body length), and the percentage difference established for each organ. The algebraic difference between these percentage results for the control and the test rat in each case is taken as indicating the percentage of change in the corresponding organ. Therefore, the average percentage changes for the organs in the fourth column in table 1 are calculated by a method different from that in the first three columns of the table, where the absolute data for test rats and controls are directly compared. In making the comparisons of organs, the very slight differences in body weight (not exceeding 2 per cent) between test rats and controls in each group were ignored.

For economy of space, only the average data are given in table 2. The sexes were at first grouped separately, but were later combined in all cases excepting those with marked sexual difference in weight (hypophysis, suprarenals, and gonads). The individual data will be filed later in The Wistar Institute of Anatomy, Philadelphia, where they may be obtained if desired.

On account of the relatively small number of observations, it is evident that the results for the various organs may be influenced by individual variation and experimental error, hence they are not to be considered final. Where the changes are marked and constant, however, they indicate the result with a considerable degree of probability; and vice versa, when the tests and controls differ but slightly, we may assume it as probable that the earlier inanition has had no marked effect upon the relative or proportional size of the organ at the end of the refeeding period.

EFFECTS ON BODY WEIGHT

The effects of the underfeeding and subsequent refeeding upon the body weight in the various groups are shown by the curves in charts 1 to 5. Chart 1 shows the composite curves for the eight litters underfed from birth to three weeks of age, including 11 test males, 12 test females, 6 control males and 4 control females. The normal difference in weight according to sex is evident. The sudden rise in the curves for the controls at about 300 days of age is due to the death of individuals with abnormally low body weights, causing previous depression of the curves. Although in five of the twenty-three test rats (table 1) the maximum body weight reached or exceeded slightly that of the controls of the same sex in the same litter, the average for the test rats for each sex remains definitely below that of the controls.

The curves of body weight for the rats refed after underfeeding from birth to six weeks of age are shown in chart 2. This is a small group, the males including 1 test and 1 control rat from litter St. 61, the females including 2 test and 2 control rats from litters 52 and 71 (table 1). Although the normal maximum body weight was not reached by either male or female controls (in the former, on account of a wounded foot), they remain at all times above the test rats of corresponding sex, as shown by the chart and by table 1.

In chart 3 are shown the curves of body weight for the rats refed after underfeeding from birth to about ten weeks (average 72 days) of age. They include nine litters, with 10 test males, 9 test females, 8 control males, and 3 control females (table 1). The sudden rise in the curve for control males at 490 days is not due to an actual increase in body weight, but to the survival of a single rat of unusually large size. Similarly in the test females, the continued rise in body weight after 340 days is due partly to the elimination of one rat (St. 111.8) which was very low in final weight, and to the survival of an unusually large test rat (St. 111.4). The final gross body weight of the latter (212 grams) was 1 gram above that of the surviving control (St. 111.5). In no other case did the maximum body weight of a test rat in this group reach that for the control of the same sex in the same litter. Even in this case, the net body weight (gross weight minus intestinal contents) of the test rat was 191 grams, while that of the control was 198 grams. Both were pregnant when killed. Except at this point, the average body weights for the test animals, as shown by the chart and by table 1, remain definitely below those for the controls of the same sex.

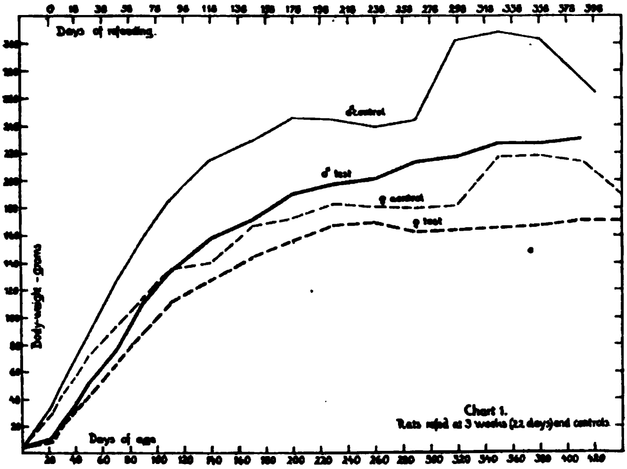

Chart 1.
Rats refed at 3 weeks (22 days) and controls.

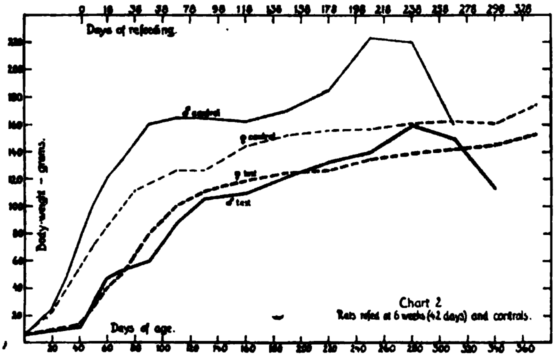

Chart 2.
Rats refed at 6 weeks (42 days) and controls.

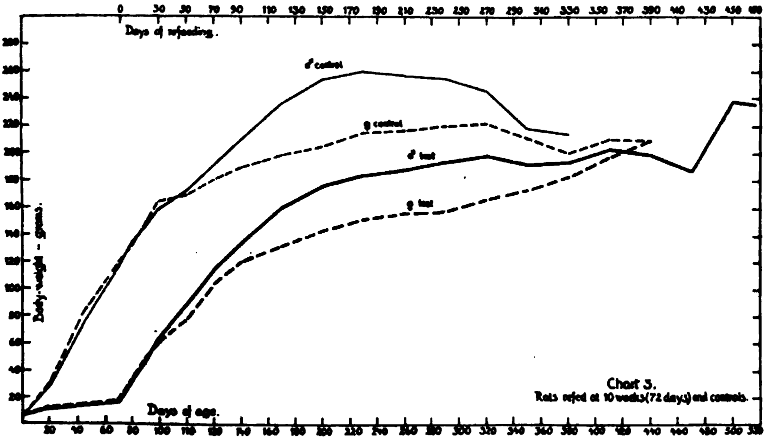

Chart 3.
Rats refed at 10 weeks (72 days) and controls.

Chart 4 represents the individual curves of body weight for five albino rats from litter S33, refed after underfeeding beginning at three weeks and extending up to twenty weeks (138 days) of age. The test rats included 2 males and 1 female, with 1 male and 1 female full-fed control (table 1). 'L' indicates the birth of a litter by the female control. While the test rats grew rapidly for awhile after refeeding, the growth soon ceased and their permanent depression in body weight, in comparison with that of the controls, is obvious.

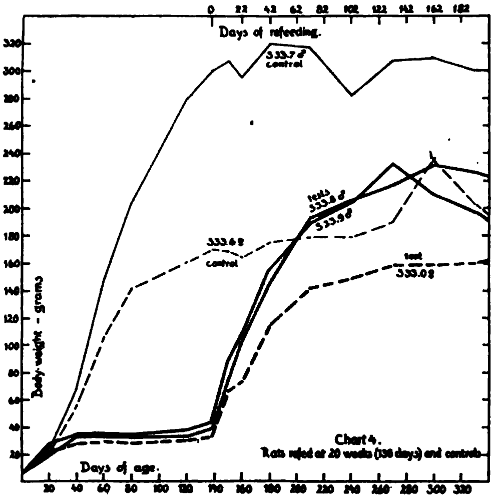
Chart 4.
Rats refed at 20 weeks (138 days) and controls

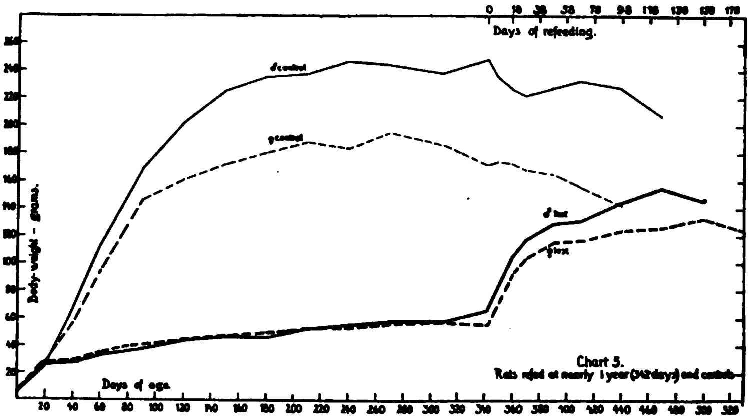
Chart 5.
Rats refed at nearly 1 year (342 days) and controls

TABLE 1

Individual data for the gross body weight of normal controls and test rats refed after underfeeding for various periods

RAT NUMBER AND SEX	REFED AT		MAXIMUM WEIGHT	FINAL		TERMINUS * = AUTOPSY	NUMBER OF PREGNANCIES
	Age	Weight		Weight	Age		
	A. Rats underfed from birth, and normal controls						
	days	*grams*	*grams*	*grams*	*days*		
St 134.1 m	(Control)		236	226	288	Died	
St 134.3 m	21	10.3	193	159	330	Died	
St 134.5 f	21	10.6	151	141	395	*Killed	0
St 134.6 f	21	10.7	174	167	452	*Killed	0
St 122.2 m	(Control)		345	337	380	*Killed	
St 122.8 m	22	10.8	230	224	409	*Killed	
St 122.6 f	(Control)		248	231	422	*Killed	3
St 122.1 f	22	10.5	208	186	422	*Killed	3
St 49.1 m	(Control)		273	239	270	(?)	
St 49.2 m	22	11.0	180	179	270	Died ?	
St 49.3 m	22	11.6	176	173	270	Died ?	
St 49.4 f	22	13.0	180	125	216	Died	2
St 70.5 m	(Control)		188	133	321	Died	
St 70.1 m	22	11.5	186	170	302	Died	
St 70.2 m	22	11.3	202	174	356	Died ?	
St 70.3 f	(Control)		208	190	440	Alive	2
St 70.4 f	22	12.5	201	158	440	Died	2
St 125.4 f	(Control)		173	156	323	Died ?	0
St 125.2 f	22	9.8	167	165	323	Died ?	0
St 125.5 f	22	9.0	173	168	488	Died	0
St 140.7 m	(Control)		244	244	147	Died	
St 140.8 m	21	9.0	218	207	388	Died	
St 140.3 f	(Control)		177	173	325	Died	1
St 140.1 f	21	10.0	192	176	458	Alive	0
St 140.5 f	21	9.5	201	181	458	Alive	1
St 148.3 m	(Control)		287	264	423	Alive	
St 148.1 m	21	9.2	130	130	197	Died	
St 148.7 m	21	9.5	269	243	423	Alive	
St 148.8 m	21	9.9	252	222	423	Alive	
St 152.6 m	21	9.1	177	177	184	Died	
St 152.2 f	21	10.2	185	156	400	Alive	1
St 152.5 f	21	10.5	187	160	400	Alive	0
St 152.8 f	21	10.5	166	166	184	Died	1
St 86.5 m	(Control)		298	215	446	Died	
St 86.2 m	28	13.0	206	184	549	*Killed	
St 61.5 m	(Control)		223	154	314	Died ?	
St 61.3 m	42	12.2	160	113	341	Died ?	
St 71.7 f	(Control)		175	175	369	Alive	2
St 71.2 f	42	13.2	158	153	369	Died	0

TABLE 1—*Continued*

RAT NUMBER AND SEX	REFED AT		MAXIMUM WEIGHT	FINAL		TERMINUS * = AUTOPSY	NUMBER OF PREGNANCIES
	Age	Weight		Weight	Age		
A. Rats underfed from birth, and normal controls							
	days	*grams*	*grams*	*grams*	*days*		
St 52.7 f	(Control)		160	152	345	*Killed	0
St 52.4 f	42	12.2	140	130	345	*Killed	0
St 146.7 m	(Control)		295	220	340	Died	
St 146.5 m	60	16.0	205	172	408	Alive	
St 146.6 m	60	16.0	251	203	441	Alive	
St 145.2 m	(Control)		251	246	410	Died	
St 154.4 f	61	16.8	174	167	410	*Killed	1
St 145.5 f	61	16.0	188	183	410	*Killed	1
St 76.6 m	(Control)		280	251	357	Alive	
St 76.8 m	(Control)		310	260	357	Alive	
St 76.6 m	70	15.6	171	142	357	Alive	
St 76.9 f	(Control)		238	234	357	Alive	4
St 76.10 f	70	17.0	152	140	357	Alive	0
St 73.6 m	(Control)		187	187	180	Alive	
St 73.7 m	70	12.7	103	103	153	Died	
St 73.2 f	70	16.5	87	87	153	Died?	0
St 65.6 m	(Control)		217	167	291	Died	
St 65.4 m	70	14.9	158	135	500	Died	
St 65.9 m	70	14.9	138	138	186	Died	
St 65.10 f	(Control)		196	196	174	Died	0
St 65.2 f	70	15.0	117	117	186	Died	0
St 138.6 m	(Control)		283	223	390	Alive	
St 138.1 m	70	15.6	208	149	357	Died	
St 111.3 m	(Control)		247	115	448	Died	
St 111.9 m	69	16.0	243	236	536	*Killed	
St 111.1 m	69	15.5	182	182	321	(?)	
St 111.5 f	(Control)		211	211	465	*Killed	4
St 111.8 f	69	16.0	181	149	351	Died?	3
St 111.4 f	69	13.8	212	212	465	*Killed	4
St 173.1 f	80	17.0	136	136	326	Alive	0
St 173.3 f	80	16.0	126	120	326	Alive	0
St 180.5 m	83	16.5	237	237	315	Alive	
B. Rats underfed from age of three weeks, and normal controls							
S 33.7 m	(Control)		316	307	346	*Killed	
S 33.9 m	138	43.0	236	191	335	*Died	
S 33.8 m	138	38.5	233	229	346	*Killed	
S 33.6 f	(Control)		233	194	339	*(?)	1
S 33.0 f	138	32.5	162	162	339	*(?)	0
S 16.0 m	(Control)		243	176	261	*Died?	
S 16.1 m	255	53.0	119	94	368	Died	

TABLE 1—*Concluded*

RAT NUMBER AND SEX	REFED AT		MAXIMUM WEIGHT	FINAL		TERMINUS * = AUTOPSY	NUMBER OF PREGNANCIES
	Age	Weight		Weight	Age		
B. Rats underfed from age of three weeks, and normal controls							
	days	*grams*	*grams*	*grams*	*days*		
S 16.6 f	(Control)		162	158	275	Alive	3
S 16.4 f	255	58.0	127	111	321	Died	0
St 20.4 m	(Control)		263	183	474	Died	
St 20.8 m	330	60.5	125	114	493	*Died	
St 38.3 m	(Control)		210	197	288	Died	
St 38.4 m	331	63.0	187	168	519	*Killed	
St 38.6 f	331	45.0	120	100	443	*Killed	0
St 32.5 f	358	58.0	114	108	490	*Killed	0
St 41.6 m	(Control)		293	270	310	*Killed	
St 41.4 f	310	52.5	137	100	399	*Died	2
St 19.8 f	(Control)		201	151	305	*Killed	4
St 19.5 f	331	78.5	130	121	532	*Killed	0
St 25.8 m	(Control)		281	228	298	Died?	
St 29.7 m	(Control)		290	197	365	*Died	
St 29.2 m	331	59.0	157	143	492	*Killed	
St 29.9 f	(Control)		184	168	188	*Died	1
St 29.6 f	331	54.0	129	119	436	*Died	0
M 9.11 m	(Control)		285	213	400	Died	
M 9.9 m	332	72.0	171	119	425	Died	
St 46.9 m	335	48.0	158	146	489	Alive	
St 46.2 f	335	56.3	157	157	489	Alive	0
St 46.5 f	335	52.6	98	98	412	Died	0
St 36.2 m	(Control)		267	255	475	*Killed	
St 36.3 m	366	69.5	118	85	442	*Died	
St 33.1 m	(Control)		252	196	493	*Killed	
St 33.4 m	375	61.0	167	147	529	*Killed	
St 34.7 m	(Control)		241	199	401	*Killed	
St 34.6 m	374	52.4	181	154	484	*Killed	
St 35.2 m	368	56.5	122	119	418	*Died	
St 35.6 f	(Control)		171	141	477	*Killed	3
St 35.4 f	368	60.5	146	125	501	*Died	0
St 35.5 f	368	52.0	141	125	524	*Killed	0
St 35.7 f	368	45.0	104	91	438	*Died	0
St 24.7 f	(Control)		210	181	344	*Died	1
St 26.9 f	(Control)		235	197	343	*Killed	3

In chart 5, the average body weight curves are shown for the albino rats refed after underfeeding from three weeks up to nearly a year (average 342 days) of age. Rats from sixteen litters are included, with 10 test males, 11 test females, 10 control males, and 6 control females. In no case did the maximum body weight of an individual test rat approach that of the corresponding control of the same litter and sex (table 1). As shown by the curves, the underfed rats grew rapidly for a time after refeeding, but were permanently stunted and unable to attain the normal adult body weight, although amply refed until growth had ceased.

While there is clearly a permanent stunting in the body weight of the rats as a result of the earlier period of underfeeding, it is difficult to measure the amount of depression on account of irregularities in the various curves, as shown in charts 1 to 5. Measured roughly, however, it may be said that the shortage in ultimate body weight in the test rats varies from about 10 per cent in chart 1 to about 35 per cent in chart 5. We may consider the dwarfing effect of inanition in general as varying according to, 1) the length of the underfeeding period; 2) the age at which the inanition occurs; 3) the sex; 4) the severity, and, 5) the character of the inanition.

As to the length of the inanition, it is found, as might be expected, that in general the longer the period of starvation in the young animal, the more marked is the depression in ultimate body weight. This is not so clear in charts 1, 2, and 3, as in charts 4 and 5. The curves of Stewart ('16) show complete recovery of rats fully refed after a period of maintenance (at constant body weight) by underfeeding beginning at three weeks and extending up to four, six, or ten weeks of age. (The males at ten weeks formed an exception, which will be considered later). The present experiments show that if the underfeeding beginning in rats at the same age (three weeks) is extended up to twenty weeks, even allowing a moderate increase in the body weight, there is a marked permanent depression of the ultimate body weight, as shown in chart 4. If the underfeeding is prolonged to nearly a year, the effect is still greater, the ultimate body weight of the refed survivors being more than one-third below that of the normal controls.

This result is in general agreement with Aron ('14), who found that if the underfeeding of young rats is prolonged beyond 50 to 150 days, the rats upon full refeeding fail to reach their normal size and weight, thus remaining permanently stunted or dwarfed. Aron therefore concluded that full recovery upon refeeding is possible only when the retardation of the growth has not extended beyond the time of the normal active growth period.

Brüning ('14) found that young nursing rats underfed by removal from the mother for successive periods are greatly retarded in later growth. The normal body weight was not fully recovered upon subsequent full feeding, but the experiment was not continued long enough to determine whether the effect was permanent.

Hatai ('07), however, observed complete recovery of normal body weight on refeeding after partial starvation (starch diet) for three weeks in rats one month old. Stewart ('16) also obtained similar results in rats refed after maintenance (constant body weight) by underfeeding from three to ten weeks of age.

Osborne and Mendel ('14, '15), in an extensive series of experiments upon the growth of rats with various inadequate protein diets, likewise found a remarkable capacity for full recovery of body weight upon proper refeeding, even after growth has been suppressed for periods of time (up to 558 days) far beyond the normal growth period. They claim that the capacity to resume growth does not depend upon the size or age at which the inhibition of growth is effected, and state that: "It is now reasonable to ask whether the capacity to grow can ever be lost unless it is exercised." A considerable number of cases, with growth curves, are presented to support this conclusion. These are chiefly rats in which growth was retarded by qualitatively deficient (inadequate protein) diets, which will be discussed later. In one case, however, a female rat in which growth was repressed by 'limited quantity of food' (no further details given), the body weight of 53 grams at 39 days of age reached only 59 grams at 513 days. Rapid growth ensued upon full refeeding, the body weight reaching 220 grams, which is above the normal maximum, in about 130 days. Unfortunately, no direct controls from the same litters were kept in the experiments of Osborne and Mendel. They admit that "resumption of growth has not been as perfect in every case as in the typical records here presented," but the positive results are considered more valuable, since failure may be due to various causes. Their results will be referred to again later.

As to the variation in the effect of inanition according to the age of the animal, it is evident from charts 1 and 2 that underfeeding beginning at birth produces permanent stunting, whereas Stewart ('16) found that an equal (or greater) degree of underfeeding for similar periods beginning at three weeks of age is followed by complete recovery of body weight upon later full refeeding. As previously mentioned, Brüning likewise apparently obtained a permanent retardation of growth of nursing rats. It is not strange to find that a permanent stunting is more readily obtained in younger animals (probably likewise in the human species), when the normal growth process is most active and the organism in general is less resistant to starvation. The greater power of recuperation found by Osborne and Mendel is probably due in part to the fact that their rats were underfed beginning usually at five weeks or more of age, at which time their resistance to inanition is greater.

In this connection it is of interest to note that both Dunn ('08) and King ('16) found that rats greatly undersized at birth, although they may grow vigorously for a time, usually fail to reach the normal adult size. In these cases, King assumes that "The normal action of growth factors is inhibited from the very beginning of postnatal life by unknown constitutional causes, not by environmental conditions." It seems to be quite possible that in such cases the small size at birth may be due to prenatal malnutrition, which might be expected to exert a more detrimental effect during the earlier stages of the organism.

As to sex, it appears from the present experiments that in general the depression in permanent body weight by early inanition is relatively greater in the males than in the females. This is evident in all the charts, 1 to 5. It is also in agreement with the observation by Stewart ('16), who found that in rats held at maintenance by underfeeding from three to ten weeks of age, the females made full recovery upon refeeding, while the males apparently did not. On the other hand, there is no evidence to indicate that the mortality is markedly greater among the males during the inanition period, since the survivors of the experiments are about equally distributed according to sex.

Since the ultimate body weight is affected by the bearing of young (Watson, '06), this factor must be considered. The pregnancies occurring in each group of the present series are given in the following table:

EXPERIMENT	TEST FEMALES			CONTROL FEMALES		
Refed after underfeeding from	Number of rats	Number pregnant	Total number of pregnancies	Number of rats	Number pregnant	Total number of pregnancies
Birth to 3 weeks	12	6	10	4	3	6
Birth to 6 weeks	2	0	0	2	1	2
3 to 10 weeks	9	4	9	3	2	8
3 to 20 weeks	1	0	0	1	1	1
3 weeks to 1 year	11	1	2	6	6	15
Total	35	11	21	16	13	32

It is evident from the table that although opportunity for breeding was equally good in the test rats, their reproductive capacity was very decidedly reduced. This is especially striking in the last two groups, where only one of the twelve test females became pregnant at all; whereas all of the seven control females became pregnant, bearing a total of sixteen litters.

Watson ('05) found that the body weight of female albino rats bearing young (three litters) averages about 9 per cent greater than in unmated female controls. This agrees closely with the results of Minot ('91) for guinea-pigs. This might be sufficient to account for the difference between the test and the control females in charts 1, 2, and 3, if all the controls had borne young and all the test rats were virgins. As shown in the table above, however, this was not the case, although pregnancies were considerably more frequent in the control rats. In the rats which had undergone prolonged inanition (charts 4 and 5), pregnancy occurred very rarely, as above shown, but in these the excess weight of the control is far greater than could be explained by their bearing of young. It is evident, however, that if the female control rats had borne no young their weight would have been slightly less and therefore somewhat nearer to that of the test rats. The contrast between the results in male and female emphasizes the difference between the sexes in their depression of ultimate body weight as a result of an early period of underfeeding.

The question as to whether the dwarfing of the body produced by inanition could be transmitted by heredity (in the few cases where reproduction occurs) is of considerable interest. In the present series, however, records are available only in the case of the one female (St. 41.4) which bore young after the long underfeeding period (3 weeks to 310 days). This extreme case might be expected to show such an effect if any were possible. This female reached a maximum of only 138 grams in bodyweight. Mated with a normal male (of the same litter), she bore two litters. One of these, litter no. 133a, was kept under observation. The litter included four males and two females, of normal size at birth. One male died early; the others reached adult maximum body weight of 215, 226, and 244 grams. The two females reached maximum of 174 grams and 204 grams, both being pregnant at the time. Thus they were slightly below the normal maximum weight, and each bore only one litter, but this is not unusual even among the control rats (table 1). The two females and one male were alive and apparently normal at fourteen months of age. The results therefore do not indicate the transmission of any marked hereditary effect of inanition, though further observations would be necessary to establish any definite conclusion on this point. The result might of course be slight, but cumulative in successive generations.

There is also unquestionably a difference in the effect of underfeeding upon the ultimate growth of the body, depending upon the severity of the inanition. As is well known, short periods of inanition, even sufficiently severe to repress growth temporarily, do not prevent the attainment of full adult size on subsequent refeeding (Hatai, '07; Stewart, '16). The favorable results obtained by Osborne and Mendel ('14, '15, '17) upon refeeding after longer periods of inanition may be due in part to the fact that in most cases their rats were not only older at the beginning of the experiment, but were allowed to increase during the experiment to a body weight considerably greater. That is, the inanition was somewhat less severe than in our present series. This perhaps also accounts for the fact that Osborne, Mendel and Ferry ('17) found no decrease of reproductive capacity in their female rats when amply refed after an extensive earlier period of stunting.

It should be emphasized that the present experiments represent very extreme degrees of underfeeding, at which even with the greatest care many of the rats perish from inanition. Thus the rats underfed from birth so as to restrict their body weight to 15 or 16 grams at ten weeks would be roughly comparable to children about twelve years of age so stunted by underfeeding from birth as to reach a body weight of about 20 pounds, normally reached at one year. Similarly, a rat underfed from three weeks to nearly a year (340 days) of age at about 60 grams body weight would correspond roughly to a human of adult age dwarfed by underfeeding from infancy so that the body weight would not exceed that of a normal child below the age of puberty.

Finally, there is doubtless a difference in the effect according to the character of the inanition, particularly in inanition due to qualitative deficiencies in the diet. Aron ('14) found that a protein-poor diet appeared to affect more unfavorably the subsequent growth of rats upon later refeeding than did a corresponding degree of underfeeding with restricted amounts of a normal diet. On the contrary, as previously mentioned, Osborne and Mendel ('14, '15) obtained complete recovery of body weight upon proper refeeding of albino rats in which growth had been almost completely suppressed for long periods by various inadequate protein diets. It is quite possible that such diets fed in abundant amounts may have less injurious effects upon subsequent growth capacity than does the feeding of restricted amounts of a balanced ration. Mendel ('14) has especially emphasized the difference between their experiments, in which the diet was ample in calories, and those of simple underfeeding with restricted amounts of a balanced diet. The relation of inanition to other factors producing abnormalities of growth is discussed by Mendel ('17).

It is also possible, however, that the very surprising results of Osborne and Mendel may be in part explained in another way. It is known that individual rats (and perhaps individual strains) may vary greatly in their resistance to inanition and in capacity for recuperation. In the experiments of Osborne and Mendel, it appears that some individuals are able to maintain their capacity for growth under conditions which would probably in most cases produce a permanent stunting or dwarfing of the body. To what extent this may be true in their experiments is uncertain, since they do not state the total number of animals under experiment, from which the successful cases were selected.

In our experience, as above stated, a large percentage of the animals die during the course of the severe underfeeding experiments, either directly from inanition or indirectly through lowered resistance to disease. Practically all of the survivors appear permanently stunted in their ultimate capacity for growth, although many of them upon autopsy reveal no evident disease. Accordingly, there seems no escape from the conclusion that while a considerable degree of inanition during growth may be followed by prompt and complete recovery upon ample refeeding, more severe and prolonged underfeeding, especially in the very young, reduces materially their capacity for subsequent growth and usually results in permanently dwarfed individuals.

BODY LENGTH AND TAIL LENGTH

The observations of Stewart ('18) indicate that at the end of the underfeeding period in young rats there is a relative elongation of the body (nose-anus) length, as compared with that in normal controls of the same body weight, amounting to an average of about 6 per cent in those underfed from birth to ten weeks, and about the same in those underfed for long periods beginning at three weeks of age. Jackson and Stewart ('19) have shown that in the case of the rats underfed from birth, the body length is still above normal on full refeeding to a body weight of 25 grams, but about normal in those refed to 50 or 75 grams. The present data (table 2) show the body length slightly subnormal (4.5 to 5.5 per cent) in such rats when refed for longer periods to maximum body weight. This means that in the test rats the body is relatively slightly plumper than in the controls. In the group refed after the longest period of underfeeding, however, as shown in the fourth column of table 2, there is practically no difference in body length between test rats and controls. It is therefore apparent that in any case no trace of emaciation remains in the underfed rats after refeeding to their maximum body weight.

The tail length in the rats underfed from birth increases even more than the body length (Stewart, '18), so the rats are relatively long-tailed at the end of the underfeeding period. On ample refeeding of such rats to a body weight of 25 to 75 grams, Jackson and Stewart ('19) find the ratio of tail length to body length nearly normal. The present data (table 2), however, indicates that in such rats, as well as those starved for longer periods, on amply refeeding to maximum body weight the tail becomes relatively somewhat short, averaging 4 to 8 per cent shorter than in the normal controls of the various groups. There is a slight sexual difference in tail length (that of the female being relatively slightly longer), but since the difference between test and control rats appeared nearly equal in each sex, the sexes are combined in the table.

TABLE 2

Average data for the parts, systems, and organs in the groups of albino rats fully refed to permanent size (adult) after underfeeding for various periods. Percentage differences (+ or —) between the data for test rats and for normal controls of similar body weight are indicated in parentheses. See note on the fourth group

	UNDERFED FROM BIRTH TO 3 WEEKS AND REFED	UNDERFED FROM BIRTH TO 10 WEEKS AND REFED	UNDERFED FROM 3 WEEKS TO 20 WEEKS AND REFED	UNDERFED FROM 3 WEEKS TO NEARLY 1 YEAR AND REFED
No. of test rats...	2 males, 3 fem.	1 male, 3 fem.	2 males, 1 fem.	7 males, 8 fem.
No. of controls...	4 males, 8 fem.	7 males, 9 fem.	5 males, 9 fem.	4 m, 8 f.[1]
Age of test rats...	445 da. (+18.0)	453 da. (+16.1)	340 da. (−12.2)	490 da.[1]
Body weight, g. ..	180 (−0.3)	200 (−2.0)	192 (+1.1)	129[1]
Body length, mm..	187 (−4.5)	190 (−5.5)	189 (−4.5)	176 (−0.2)
Tail length, mm...	159 (−8.0)	164 (−6.5)	163 (−5.9)	147 (−4.0)
Head, g...........	16.7 (−6.2)	18.5 (−1.6)	18.3 (−0)	14.6 (+6.6)
Fore limbs, g.....	11.7 (+4.5)	13.1 (+6.5)	11.9 (−1.7)	8.6 (+19.4)
Hind limbs, g.....	26.5 (−0.4)	29.8 (−1.9)	27.9 (−1.1)	19.7 (−1.5)
Trunk, g.........	121 (+1.7)	127 (−5.2)	128 (+1.6)	79.2 (−11.1)
Integument, g. ...	30.3 (−5.6)	33.7 (−7.4)	36.8 (+9.8)	22.5 (−7.8)
Skeleton, lig., g .	20.1 (−2.4)	19.3 (−11.9)	20.5 (−3.3)	16.1 (+5.2)
Skeleton, cart., g..	15.5 (−15.3)	14.6 (−24.7)	17.3 (−7.0)	14.1 (—)
Musculature, g...	71.8 (−4.1)	75.8 (−10.3)	83.9 (+5.8)	49.0 (−8.6)
Visceral group, g.	26.2 (+9.9)	26.0 (+3.6)	27.5 (+13.2)	20.1 (−3.8)
'Remainder,' g....	25.2 (+11.0)	33.5 (+26.9)	16.2 (−33.3)	14.4 (−11.7)
Brain, g..........	1.577 (−8.0)	1.679 (−4.2)	1.726 (−0.6)	1.690 (+2.8)
Spinal cord, g. ...	0.555 (−6.7)	0.605 (−1.3)	0.587 (−2.3)	0.514 (−0.9)
Eyeballs, g.......	0.319 (−2.1)	0.332 (+1.2)	0.292 (−10.7)	0.319 (+18.0)
Thyroid, g........	0.0297 (+23.2)	0.0240 (−5.5)	0.0234 (+13.1)	0.0153 (−13.2)
Thymus, g........	0.0409 (−29.9)	0.0542 (−12.2)	0.1029 (+85.7)	0.0439 (−7.8)
Hypophysis, m., g.	0.0077 (−7.2)	0.0081 (−10.0)	0.0092 (+8.2)	0.0058 (−15.3)
Hypophysis, f., g..	0.0112 (−2.6)	0.0101 (−18.5)	0.0094 (−24.2)	0.0068 (−5.7)
Pineal body, g.....	0.0018 (+20.0)	0.0015 (+7.1)	0.0009 (−40.0)	0.0012 (—)
Heart, g..........	0.852 (+8.7)	0.841 (+1.2)	0.934 (+14.9)	0.646 (+7.5)
Lungs, g..........	3.19 (−11.9)	2.87 (−14.3)	2.96 (−15.2)	4.94 (+31.4)
Liver, g...........	7.92 (+6.3)	8.27 (+3.4)	9.22 (+19.9)	5.09 (+8.5)
Spleen, g..........	0.637 (+11.8)	0.647 (+8.2)	0.516 (−12.6)	0.387 (−7.0)
Kidneys, g........	1.660 (+3.4)	1.623 (−7.4)	2.060 (+22.5)	1.186 (−0.9)
Stomach—intestines with contents, g.........	13.83 (+15.1)	17.42 (+32.2)	14.41 (+14.0)	10.48 (—)
St.-Int., empty, g.	7.05 (+17.3)	8.42 (+27.6)	7.09 (+12.7)	4.41 (−3.3)
Suprarenals, m., g.	0.0374 (−17.6)	0.0370 (−11.1)	0.0479 (+10.6)	0.0362 (+4.5)
Suprarenals, f., g..	0.0499 (+1.5)	0.0563 (+12.6)	0.0396 (−20.8)	0.0400 (+17.8)
Ovaries, g.........	0.0451 (−35.5)	0.0306 (−56.8)	0.0482 (−32.0)	0.0355 (−61.5)
Testes, g.	1.805 (+8.7)	2.232 (+17.6)	2.307 (+30.3)	1.667 (+17.1)
Epididymides, g...	0.613 (+22.8)	0.745 (+32.6)	0.637 (+24.4)	0.512 (+34.0)

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[1] In the fourth group, comparisons between test rats and controls for the organs were made through the Wistar norms by Donaldson's method. For the body parts and systems, the normal was calculated from the data of Jackson and Lowrey, as explained in the text.

HEAD, LIMBS AND TRUNK

In rats underfed from birth to three weeks of age, Stewart ('18) found the head about 16 per cent above normal weight, but in those underfed to six or ten weeks the head was nearly normal. In such underfed rats, on ample refeeding to a body weight of 25 to 75 grams, Jackson and Stewart ('19) found the head weight nearly normal. Similarly in the present series (table 2), refed to maximum body weight, the head weight is nearly normal, the relatively small differences being probably of no significance.

The limbs and trunk show no marked or constant change in relative weight during the underfeeding period in young rats (Stewart, '18), and likewise during ample refeeding up to body weights of 25 to 75 grams (Jackson and Stewart,'19). Similarly in the present series, the limbs and trunk in general show no marked deviation from the normal weight, except in the last group (table 2, fourth column). Even in this case, the excess weight of the fore limbs (+19.4 per cent) and the subnormal weight of the trunk (−11.1 per cent) are of questionable significance. The limbs are difficult to separate from the trunk in a uniform way, and, as previously explained, no direct controls were available for this group. On the whole, therefore, it is doubtful whether the refed test rats show any significant abnormality in the proportions of their head, limbs, or trunk.

THE BODY SYSTEMS

These body systems include the integument, skeleton, musculature, visceral group, and 'remainder.'

Integument. In rats underfed from birth, Stewart ('16) found the integument nearly normal in weight at three weeks, but 43 to 48 per cent subnormal at six and ten weeks of age. On refeeding such rats, Jackson and Stewart found the integument still subnormal at a body weight of 25 grams, but normal (or above) at 50 and 75 grams. The present series (table 2) shows the integument averaging slightly subnormal (−5.6 to −7.8 per cent) in all, but the third group (+9.8 per cent). The differences are of questionable significance, as the skin is quite variable in weight, but it would seem that the relative plumpness of the body (above referred to) is not due to accumulation of subcutaneous fat.

Skeleton. The 'ligamentous skeleton' includes the bones, cartilages, periosteum, and ligaments. The fibrous structures were removed by maceration (see earlier papers for technique), leaving the 'cartilaginous skeleton,' which was oven-dried to constant weight as the 'dry skeleton.'

A remarkably persistent overgrowth of the skeleton in general has been observed during underfeeding in calves (Waters, '08), puppies (Aron, '11) and rats (Jackson, '15). Increase in body length, indicating continued increase in skeletal growth, with retardation in body weight, has also been noted in malnourished human infants and children (Variot, '07; Freund, '09; Birk, '11; Hess, '16). In rats underfed from birth, Stewart ('18) found at three to ten weeks an excess weight of 19 to 24 per cent in the ligamentous skeleton, 33 to 94 per cent in the cartilaginous skeleton, and 46 to 166 per cent in the dry skeleton. In such rats, on ample refeeding to 25 to 75 grams in body weight, Jackson and Stewart ('19) found that in general the skeletal weight has dropped to normal proportions, or even subnormal (cartilaginous and dry skeleton), suggesting that although skeletal growth persists during early inanition periods, its later growth may be inhibited. The present data (table 2) tend to confirm this in the test rats amply refed to maximum body weight. While the condition in the last group is more uncertain (due to lack of direct controls, as previously explained) the other groups show uniformly subnormal skeletal weight. While small in the ligamentous skeleton (−2.4 to −11.9 per cent), it is more definite in the cartilaginous skeleton (−7.0 to 24.7− per cent), which probably accounts for the slightly subnormal body length. A few observations on the weight of the dry skeleton (not given in the table) show a slight deficit in the test rats, but they are too few to be conclusive.

Musculature. In rats underfed from birth to three, six, or ten weeks of age, Stewart ('18) found the musculature slightly (8 to 12 per cent) above normal weight. In such rats, on ample refeeding to a body weight of 25 to 75 grams, Jackson and Stewart ('19) found no excess, but rather a slight deficit (−5.7 to −15.4 per cent) in the musculature of the rats underfed to six or ten weeks. This indication that early inanition may exert a retarding effect on the later growth of the musculature is to a certain extent supported by the present data for such rats refed to maximum body weight. As shown in table 2, there is a slight underweight (−4.1 to −10.3 per cent) in all except the third group, which instead averages 5.8 per cent above normal. These differences are so slight that their significance is somewhat doubtful, though a negative tendency is apparent.

Visceral group and remainder. The visceral group, which includes all the individual organs listed in table 2, is found 28 to 38 per cent above normal weight in young rats underfed from birth to three, six, or ten weeks of age (Stewart, '18). Jackson and Stewart ('19) found the group as a whole nearly normal in weight when such rats were amply refed to a body weight of 25 to 75 grams. The present data (table 2) show the visceral group slightly above normal weight (+3.6 to +13.2 per cent) in all but the last column (−3.8 per cent). There are differences in the individual organs, however, as will be discussed later.

The 'remainder' is obtained by deducting from the net body weight (intestinal contents excluded) the weight of the integument, skeleton, musculature, and visceral group. This 'remainder' includes various small, unweighed organs, dissectible fat, body fluids, loss by evaporation, etc. In rats underfed from birth to three, six, or ten weeks, Stewart ('18) found a marked loss (−19 to −40 per cent) in the weight of the 'remainder.' No constant or significant variations from the normal occurred in such rats amply refed to a body weight of 25 to 75 grams (Jackson and Stewart, '19). In the present series, the 'remainder' is considerably above normal in the refed rats which had been underfed from birth, but below normal weight in those underfed beginning at three weeks of age (table 2). The interpretation is doubtful, as the 'remainder' is exceedingly variable even under normal conditions.

The individual viscera. In rats underfed from birth to three, six, or ten weeks, Stewart ('18) found in general a marked relative increase in the weights of the spinal cord, eyeballs, liver, stomach, and intestines (empty). A less marked tendency to increase occurred in the brain (especially in the earliest period), heart (progressive increase), spleen (at six or ten weeks), intestinal contents (at six or ten weeks), suprarenals (progressive increase), kidneys, testes, epididymides (at three and six weeks, loss later) ovaries and hypophysis. No marked change was found in the weights of the thyroid and pineal gland, but a definite loss of weight occurred in the lungs and especially in the thymus. In the earliest period only (up to three weeks) there was a loss in the weights of spleen and intestinal contents.

In rats underfed for very long periods (beginning at three weeks of age), Stewart found the earlier well-marked overweight still evident in the spinal cord, eyeballs, and (usually) the suprarenals. The brain showed a slight increase (above normal), and also the lungs (probably abnormal). There was apparently no marked change (or inconstant variability) in the weights of the intestinal contents, kidneys, ovaries, testes (?), and pineal body. The thyroid, thymus, heart, liver (variable), spleen (variable), alimentary canal (empty), epididymides and hypophysis (male) usually became subnormal in weight during the long underfeeding periods.

In rats underfed from birth to three, six, or ten weeks and amply refed to a body weight of 25 to 75 grams, Jackson and Stewart ('19) found considerable variation in the extent of recovery in weight among the individual viscera. The hypophysis, suprarenals, heart, lungs, and kidneys were usually normal, the liver irregular in weight. The brain, spinal cord, and thymus were almost constantly subnormal, pineal, thyroid, and epididymides somewhat irregular. The ovaries were also irregular, apparently subnormal in rats refed after underfeeding to ten weeks of age. The stomach and intestines and the eyeballs were usually somewhat above normal weight. The spleen and the testes showed an apparent overweight in the earlier stages, with a subnormal tendency later.

In the present series (table 2) the individual organs in the various groups of underfed rats refed to maximum body weight may be mentioned briefly.

The *brain*, as seen in table 2, remains subnormal (−4.2 to −8.0 per cent) in the rats refed to maximum weight after underfeeding from birth, although somewhat nearer normal than in those refed to body weight of 25 to 75 grams (previously mentioned). Thus underfeeding at this early period, while not preventing a marked temporary overgrowth of the brain (with normally proportioned parts, according to Stewart, '18 a), apparently exerts an inhibitory influence on the later growth of the brain, which is retarded so as to lag slightly behind the body as a whole in its ultimate growth in weight.

On the other hand, the longer underfeeding period beginning at the later age of three weeks is apparently less disturbing in its effects upon the growth of the brain, which is nearly normal in weight (relative to the body) both at the end of the fasting period and at the end of the refeeding period (table 2, last two columns). Hatai ('07) likewise found a normal weight for the central nervous system of rats refed after partial starvation (starch diet) for three weeks in rats one month old. King ('16), however, found both brain and spinal cord subnormal in weight in dwarfed rats which were undersized ('runts') from birth. As suggested above, this condition may possibly be due to prenatal malnutrition.

The *spinal cord*, though subnormal in weight in the rats refed to body weight of 25 to 75 grams, after underfeeding from birth (Jackson and Stewart, '19), is more nearly normal in the present series refed to maximum weight. As seen in table 2, the first group (−6.7 per cent) is the only one showing any appreciable deviation from the normal.

The *eyeballs* which grow to a remarkable extent during early inanition and are still somewhat above normal weight on refeeding to a body weight of 25 to 75 grams, are nearly normal in corresponding rats refed to maximum body weight (table 2, first two columns). Of those underfed at a later period, one group shows an underweight (−10.7 per cent), the other an overweight (+18.0 per cent) in the eyeballs, the difference being of uncertain significance.

The *thyroid gland*, which was found somewhat variable in its weight at the end of the inanition periods and on refeeding to a body weight of 25 to 75 grams, appears likewise somewhat inconstant in the present series (table 2) refed to maximum body weight. The results do not warrant any more definite conclusion.

The *thymus*, which undergoes a marked loss of weight during 'hunger involution,' was found still subnormal upon refeeding to a body weight of 25 to 75 grams (Jackson and Stewart, '19). The subnormal weight still persists in three groups of the present series, refed to maximum body weight (table 2). In one of the groups, however, there is a remarkable overweight of 85.7 per cent, probably due to experimental error in removing fat along with the thymus.

The *hypophysis* has been found by Hatai to show a sexual difference in weight, therefore the data for this gland are listed separately by sex in table 2. In most cases (excepting in the male on long underfeeding) it was found nearly normal at the end of the underfeeding periods, and on refeeding to a body weight of 25 to 75 grams. In the present series, refed to maximum body weight, it is more or less subnormal in all but one group (table 2), which shows a slight overweight (+8.2 per cent). Jackson ('17) found that in young rats refed four weeks or more after inanition the hypophysis has for the most part recovered its normal histological structure, although atrophic areas may persist for indefinite periods.

The *pineal body* was found irregular in weight in the underfed rats on refeeding to body weight of 25 to 75 grams. Likewise in the present series (table 2), it shows an apparent overweight in the first two groups, but a decidedly subnormal weight in the third. On account of the small size of the gland, no definite conclusion can be drawn from the few observations.

The *heart* shows a tendency to increase in weight in the earlier underfeeding periods, but loses weight later. It was usually found nearly normal in the rats refed to a body weight of 25 to 75 grams. In the present series, refed to maximum body weight, the heart shows a tendency to hypertrophy, which is distinct in three of the four groups (table 2), the overweight varying from 1.2 to 14.9 per cent.

The *lungs*, which were nearly normal in weight in the underfed rats refed to body weight of 25 to 75 grams, are distinctly subnormal in three of the four groups of the present series (table 2). The enormous overweight (+314 per cent) in the fourth group is undoubtedly pathological, due to a chronic lung disease, which occurs frequently in the older rats.

The *liver*, which shows a marked growth tendency during the earlier inanition periods, is variable in weight later, and in the rats refed to a body weight of 25 to 75 grams. In the present series (table 2) refed to a maximum body weight, the liver appears above normal in all groups (+3.4 to +19.9 per cent). On account of the great normal variability in the size of the liver, however, the significance of this apparent hypertrophy is somewhat uncertain.

The *spleen* is exceedingly variable in weight, both normally and after various inanition periods. In the rats refed to body weight of 25 to 75 grams, the spleen was found usually above normal in the earlier stages and subnormal later. In the present series refed to maximum body weight (table 2), the spleen appears somewhat above normal (+8.2 and +11.8 per cent) in the groups underfed from birth, but below normal (−7.0 and −12.6 per cent) in those underfed beginning at three weeks of age. It is uncertain as to how much of this difference is due merely to normal variability.

The *kidneys* were usually found normal in weight in the rats refed to a body weight of 25 to 75 grams. In the present series, refed to maximum body weight (table 2), they likewise differ but little from the normal, excepting the third group, which appears above normal (+22.5 per cent). As the kidneys normally show considerable variation in weight, this exception is of doubtful significance.

The *stomach and intestines* (without contents) show a remarkably strong tendency to increase in weight during the earlier underfeeding periods, though becoming subnormal during the later and longer fasting experiments. On refeeding (after early underfeeding) to a body weight of 25 to 75 grams, the empty stomach and intestines still appeared somewhat above normal in weight. In the present series refed to maximum body weight, an over-weight persists in the alimentary canal, both with and without contents, excepting in the fourth group (table 2). A period of inanition in the young, growing rat therefore apparently tends to produce a permanently hypertrophied condition in the alimentary canal (stomach and intestines).

The *suprarenal glands*, like the hypophysis, show a sexual difference in weight (Hatai, Jackson). They usually increase above normal weight in young rats underfed for various periods, but were found nearly normal on refeeding to a body weight of 25 to 75 grams. In the present series refed to maximum body weight, they appear irregular (table 2), some groups being above normal, others subnormal in weight. As the suprarenals are normally somewhat variable and the number of observations rather small, no definite conclusion is justified. The histological changes in the suprarenal glands during inanition and refeeding have been described by Jackson ('19).

The *ovaries* appear especially affected by inanition during the early growth period. As shown by Stewart ('18), they increase markedly in weight in rats underfed from birth to three, six, or ten weeks, but are somewhat variable in those underfed for long periods beginning at three weeks of age. In the former group, Jackson and Stewart ('19), in rats refed to a body weight of 25 to 75 grams, found the ovaries irregular in weight, usually subnormal in those which had been underfed to ten weeks.

The present data (table 2) indicate that in the rats underfed beginning either at birth or at three weeks of age, the later growth of the ovaries is profoundly affected. They average from 32 to 61 per cent below normal in the rats refed to maximum body weight. This subnormal weight of the ovaries indicates an atrophy which is doubtless sufficient to account for the marked loss of reproductive power in the test females. This was discussed earlier in the paper. Since these females were mated with normal males (the controls), their failure to reproduce cannot be ascribed to the males.

The more favorable results by Osborne, Mendel and Ferry ('17), who obtained three to five litters in four of their female rats refed after stunting by inadequate diet with retarded growth, is perhaps due to the fact that their inanition began at a later age (five or six weeks) and terminated with a body weight (90 to 108 grams) nearly double that in our rats underfed for the longest period. It is quite possible that there may be a critical period in the development of the rat's ovary, before the age of five or six weeks, when inanition is much more injurious than later.

The *testes* react somewhat like the ovaries (in weight) during the earlier inanition periods, but the ultimate effect is different. Stewart ('18) found the testes increased in weight in rats underfed from birth to three, six, or ten weeks, but variable or decreased in those underfed for longer periods beginning at three weeks of age. In the rats refed to body weight of 25 to 75 grams after underfeeding from birth, Jackson and Stewart ('19) found an apparent overweight in the testes in the earlier periods of refeeding, but a subnormal tendency later.

The present data (table 2) for the underfed rats fully refed to maximum body weight show a surprising tendency to overweight in the testes, the average varying from about 9 to 30 per cent in the various groups. Since these test males were not separately mated with normal females, it is uncertain whether their normal reproductive function was restored.

The *epididymides* in general during inanition in young rats undergo changes in weight somewhat similar to those in the testes, tending to increase in weight in early stages, with loss in weight later (Stewart). They were found irregular in weight in rats refed to a body weight of 25 to 75 grams. In the present series (table 2) in the rats refed to maximum body weight, the epididymides show a hypertrophy even greater than that of the testes, the overweight being from 23 to 34 per cent in the various groups.

SUMMARY

1. Albino rats fully refed after underfeeding from birth to three, six, or ten weeks, or from three weeks to nearly a year of age, grow variably, but usually fail to reach the normal adult size. The ultimate effect varies according to the length of the underfeeding period, the age at which the inanition occurred, the sex (body weight more affected in males), the severity and the character of the inanition.

2. In the test rats refed to maximum body weight, the body length and tail length appear slightly subnormal, head, limbs, and trunk nearly normal in weight; skeleton, integument, and musculature usually slightly subnormal, visceral group slightly above normal, and 'remainder' variable.

3. Of the individual organs, the brain, spinal cord, hypophysis, and lungs of the test rats average slightly subnormal in weight, the ovaries very markedly so. The atrophy of the ovaries probably accounts for the reduction of reproductive capacity in the test females, which is especially marked after the long underfeeding periods. The heart and alimentary tract appear slightly, and the testes and epididymides very definitely, above normal weight. The other organs appear either normal or irregular in weight, in comparison with normal controls of the same body weight.

4. While some abnormalities thus occur in the test rats, they are usually slight, and in general it may be said that the organs and parts are nearly normally proportioned in the permanently stunted rats. Thus the earlier starvation apparently retards or inhibits the later growth process of the body as a whole, with the few exceptions above noted.

LITERATURE CITED

ARON, HANS 1910 Wachstum und Ernährung. Biochemische Zeitschrift, Bd. 30, S. 207–226.

1911 Nutrition and growth. Philippine Journal of Science, B., vol. 6, Feb., pp. 1–50.

1914 Untersuchungen über die Beeinflussung des Wachstums durch die Ernährung. Berl. klin. Wochenschrift, J. 51, No. 21, S. 972–977.

BIRK, W. 1911 Unterernährung und Längenwachstum beim neugeborenen Kinde. Berl. klin. Wochenschrift, J. 48, Bd. 2, S. 1227–1231.

BRÜNING, H. 1914 Experimentelle Studien über die Entwicklung neugeborener Tiere bei längerdauernder Trennung von der säugenden Mutter und nachheriger verschiedenartiger künstlicher Ernährung. Jahrb. f. Kinderheilk., Bd. 80, S. 65–85.

DONALDSON, H. H. 1915. The rat. Reference tables and data. Memoirs of The Wistar Institute of Anatomy and Biology, no. 6, Philadelphia.

DUNN, ELIZABETH 1918 A study of the gain in weight for the light and heavy individuals of a single group of albino rats. Anat. Rec., vol. 2.

FREUND, W. 1909 Zur Pathologie des Längenwachstums bei Säuglingen. Jahrb. f. Kinderheilk., Bd. 70, S. 752–773.

HATAI, S. 1907 Effects of partial starvation followed by a return to normal diet on the growth of the body and central nervous system of albino rats. Amer. Jour. Physiol., vol. 18, pp. 309-320.

HESS, A. F. 1916 Infantile scurvy. III. Its influence on growth (length and weight). Amer. Jour. Diseases of Children, vol. 12, pp. 152–165.

JACKSON, C. M. 1915 Effects of acute and chronic inanition on the relative weights of the various organs and systems of adult albino rats. Am. Jour. Anat. vol. 18, pp. 75–116.

1915 a Changes in the relative weights of the various parts, systems and organs of young albino rats held at constant body weight by underfeeding for various periods. Jour. Exp. Zoöl., vol. 19, pp. 99–156.

1917 Effects of inanition and refeeding upon the growth and structure of the hypophysis in the albino rat. Am. Jour. Anat., vol. 21, pp. 321–358.

1919 The postnatal development of the suprarenal gland and the effects of inanition upon its growth and structure in the albino rat. Am. Jour. Anat. vol. 25, no. 3, pp. 221–289.

JACKSON, C. M., AND LOWREY, L. G. 1912 On the relative growth of the component parts (head, trunk and extremities) and systems (skin, skeleton, musculature and viscera) of the albino rat. Anat. Rec. vol. 6, pp. 449–474.

JACKSON, C. M., AND STEWART, C. A. 1918 The effects of underfeeding and refeeding upon the growth of the various systems and organs of the body. Minnesota Medicine, vol. 1, Nov.

1919 On the recovery of normal weight in the various organs of albino rats upon refeeding after underfeeding from birth for various periods. Amer. Jour. Diseases of Children, May.

KING, HELEN D. 1916 On the postnatal growth of the body and of the central nervous system in albino rats that are undersized at birth. Anat. Rec., vol. 11, no. 2, pp. 41–52.

MENDEL, LAFAYETTE B. 1914 Viewpoints in the study of growth. Biochem. Bull., vol. 3, Jan., pp. 156–176.

1917 Abnormalities of growth. Amer. Jour. Med. Sc. vol. 153, no. 1, pp. 1–20.

MINOT, C. S. 1891 Senescence and rejuvenation. Jour. Physiol., vol. 1, no. 2.

OSBORNE, T. B., AND MENDEL, L. B. (with the coöperation of E. L. Ferry and A. J. Wakeman) 1914 The suppression of growth and the capacity to grow. Jour. Biol. Chem., vol. 18, no. 1, pp. 95–106.

1915 The resumption of growth after long-continued failure to grow. Jour. Biol. Chem., vol. 23, no. 2, pp. 439–454.

1917 The effect of retardation of growth upon the breeding period and duration of life of rats. Science, N. S., vol. 45, pp. 294–295.

STEWART, C. A. 1916 Growth of the body and of the various organs of young albino rats after inanition for various periods. Biol. Bull., vol. 31, pp. 16–51.

1918 Changes in the relative weight of the various parts, systems and organs of young albino rats underfed for various periods. Jour. Exp. Zoöl., vol. 25, pp. 301–353.

1918 a Weights of various parts of the brain in normal and underfed albino rats at different ages. Jour. Comp. Neur., vol. 29, no. 5, pp. 511–528.

VARIOT, G. 1907 La dissociation de la croissance dans l'atrophie et l'hypotrophie infantiles; atrophie pondérale, atrophie staturale. Bull. et Mém. Soc. Méd. d. Hôp. de Paris, T. 24, pp. 1347–1376. (Also in Bull. Soc. de Pédiatr. de Paris, T. 9, pp. 363–369.)

WATERS, H. J. 1908 The capacity of animals to grow under adverse conditions. Proc. of the 29th Annual Meeting of the Society for the Promotion of Agricultural Science, pp. 71–96.

1909 The influence of nutrition on animal form. Proceedings of the 30th Annual Meeting of the Society for the Promotion of Agricultural Science, pp. 70–98.

WATSON, J. B. 1905 The effect of the bearing of young upon the body-weight and the weight of the central nervous system of the female white rat. Jour. Comp. Neur., vol. 15, no. 6, pp. 514–524.

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STUDIES ON THE EFFECTS OF THIRST

I. EFFECTS OF THIRST ON THE WEIGHTS OF THE VARIOUS ORGANS AND SYSTEMS OF ADULT ALBINO RATS

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THREE TABLES

CONTENTS

Material and methods 402
General observations 408
Body weight 409
Lengths of body and tail 410
Weights of organs and systems 411
Integument, skeleton, musculature, viscera and 'remainder,' brain, spinal cord, sciatic nerves, eyeballs, heart and aorta, spleen, lungs, parotid and submaxillary glands, liver, pancreas, stomach and intestines, kidneys and bladder, testes, epididymis, thyroid gland, thymus, suprarenal glands, hypophysis.
Discussion 420
Summary 430

The importance of water for the living organism is well recognized, but the effects of thirst (water inanition) have been studied only to a relatively slight extent. It has long been known that a diet deficient in water causes a loss in body weight in various species of animals, and this principle has often been followed in the treatment of human obesity. As to the effects upon the individual organs, however, but few observations have been published. The present investigation was undertaken to determine the changes in the weight of the body and of the various organs in adult albino rats subjected to a relatively dry diet for various periods. The work was done in the Institute of Anatomy at the University of Minnesota. This opportunity is taken to express my indebtedness to Dr. C. M. Jackson, Director of the Department, for valuable aid and direction.

MATERIAL AND METHODS

The albino rat (Mus norvegicus albinus) was chosen for use in this experiment. As the rat normally requires but little water in its diet, it seems (like the pigeon) to be especially suitable for thirst experiments.

The material used in the present experiments included twenty-five adult albino rats from the colony in the Institute of Anatomy. Three died during the tests, and are excluded because the coagulated blood from postmortem congestion might affect the weights of the organs. Two additional females (one pregnant) are also excluded from the tables for lack of adequate controls. The remaining twenty rats (table 1), which were killed and autopsied, are all males except one. Twelve of these were from six litters of known age (167 to 259 days). The other eight were stock rats of unknown age. Four of the rats were used for normal controls. They include the one female, which, however, is excluded in the case of organs (suprarenals, hypophysis, and gonads) that show a sex difference in weight.

The rats had all been fed chiefly upon maize, and Graham bread soaked with whole milk, with occasional fresh vegetables. They were usually placed upon a maintenance diet of whole milk and dry biscuit for some days before beginning the experiment. The biscuit used in the experiments was the 'Old Grist Mill' brand ('dog-bread') manufactured by Potter and Wrightington, Charlestown, Massachusetts, according to Castle's formula, and having approximately the following composition:

	per cent
Moisture at 100°C	4.63
Phosphates as tricalcium	6.73
Crude fiber	0.58
Proteids	15.40
Carbohydrates, starch, sugar, etc	65.57
Ether extract (fat, etc.)	7.10
Estimated calories per gram	4.6

The test rats were weighed daily and individual records kept. The temperature of the animal room was fairly constant at about 77° F. (range 65° to 80°).

Individual data for controls and test rats in the various experiments. Weight in grams; lengths in mm.

RAT NUMBER AND SEX	BODY LENGTH	TAIL LENGTH	AGE	TEST PERIOD	INITIAL GROSS BODY WEIGHT	FINAL GROSS (AND NET) BODY WEIGHT	INTEGUMENT	LIGAMENTOUS SKELETON	CARTILAGINOUS SKELETON	HUMERUS (2) AND FEMUR (2)	MUSCULATURE	VISCERAL GROUP	'REMAINDER'	BRAIN	SPINAL CORD
A. Controls															
			days	*days*											
K 3 m.	207	176	177		207	207 (202)	41.0	20.7	13.7	1.60	88.7	24.1	12.69	1.623	0.376
K 3.1 m.	195	171	177		223	223 (214)	48.5	18.3	16.5	2.64	88.7	25.1	11.26	1.722	0.559
Sr 6 m.	220	181			226	226 (216)	36.3	21.7	16.8	2.00	88.6	29.5	21.48	1.953	0.625
Sr 7 f.	193	173			193	193 (187)	34.8	19.6	15.2	1.58	80.2	22.9	17.43	1.669	0.623
B. Acute thirst															
K 4.1 m.	181	167	167	6	207	136 (133)	28.8	18.8	13.0	1.69	63.4	19.4	7.22	1.919	0.448
K 3.4 m.	195	171	189	7	220	150 (147)	31.0	19.3	14.6	1.60	58.3	19.9	5.20	1.727	0.508
Sr 8 m.	171	171		6	226	152 (148)	30.3	22.0	15.4	1.65	69.0	17.8	4.77	1.856	0.523
Si 1 m.	185	173	193	8	221	143 (136)	28.1	19.7	14.2	1.63	62.3	17.5	4.39	1.679	0.530
K 3.3 m.	196	177	189	8	224	147 (142)	34.7	19.3	15.2	1.63	57.8	20.0	2.31	1.748	0.584
K 3.2 m.	195	177	189	8	223	153 (148)	34.1	18.8	14.3	1.54	62.8	20.3	2.74	1.703	0.569
K 7.1 m.	170	161	259	15	209	118 (112)	19.8	19.2	15.2	1.74	50.9	15.1	3.81	1.762	0.582
Si 3 m.	177	174	250	16	221	119 (115)	21.7	17.8	13.3	1.64	49.9	15.5	2.63	1.749	0.488
C. Chronic thirst															
Sr 3 m.	170	171		49	208	95 (91)	20.4	16.9	12.9	1.57	34.5	11.8	1.29	1.753	0.477
K 3.5 m.	178	170	251	55	207	97 (91)	19.2	17.0	13.5	1.48	34.1	12.3	1.09	1.584	0.516
Sr 1 m.	174	164		49	209	100 (94)	20.7	17.1	14.2	1.56	31.7	17.1	1.99	1.684	0.527
K 5.1 m.	172	177		47	209	101 (96)	24.2	17.8	14.6	1.51	32.3	14.5	1.65	1.604	0.519
K 2.1 m.	171	179	244	49	212	105 (99)	22.6	19.3	14.9	1.69	32.3	14.8	1.88	1.746	0.545
Si 4 m.	183	169	243	54	209	102 (96)	20.8	19.1	15.4	1.67	33.0	15.3	2.29	1.565	0.489
Sr 2 m.	170	171		53	226	107 (102)	21.1	18.9	15.8	1.84	37.1	16.2	2.16	1.738	0.489
D. Total inanition															
Si 2 m.	181	176		11	216	114 (112)	24.1		10.3*		53.9	16.1	3.35	1.632	0.433

TABLE 1—*Continued*

Individual data for controls and test rats in the various experiments. Weight in grams; lengths in mm.

RAT NUMBER AND SEX	SCIATIC NERVES	EYEBALLS	HEART	AORTA	SPLEEN	LUNGS	PAROTID GLANDS	SUBMAXILLARY GLANDS	LIVER	PANCREAS	STOMACH—INTESTINES (FILLED)	STOMACH—INTESTINES (EMPTY)	KIDNEYS	BLADDER	TESTES
A. Controls															
K 3 m	0.046	0.307	0.825		0.557	2.56	0.149	0.533	5.77	0.815	10.8	5.85	1.66		2.07
K 3.1 m	0.054	0.289	0.884		0.514	1.48	0.162	0.453	7.69	0.979	13.6	5.01	1.86		2.24
Sr 6 m	0.064	0.334	0.834	0.116	0.844	1.78	0.170	0.480	8.16	0.984	17.0	7.59	2.10	0.119	2.68
Sr 7 f	0.043	0.283	0.733	0.143	0.594	1.96	0.135	0.381	7.98	0.793	11.6	5.58	1.93	0.098	
B. Acute thirst															
K 4.1 m	0.049	0.271	0.642		0.242	1.08	0.066	0.234	5.90	0.513	7.1	4.56	1.40		2.46
K 3.4 m	0.032	0.290	0.684		0.142	1.07	0.077	0.283	4.96	0.432	8.2	4.90	1.55		1.75
Sr 8 m	0.038	0.243	0.583		0.240	1.21	0.076	0.320	3.21	0.372	8.9	4.99	1.42		1.97
Si 1 m	0.039	0.279	0.535		0.168	0.89	0.066	0.223	4.96	0.528	8.1	3.68	1.47		1.94
K 3.3 m	0.059	0.302	0.660		0.218	1.31	0.078	0.283	5.11	0.477	10.1	4.95	1.52		2.01
K 3.2 m	0.046	0.282	0.625		0.328	0.97	0.094	0.293	5.93	0.624	10.1	4.53	1.55		1.97
K 7.1 m	0.042	0.268	0.502	0.078	0.154	1.30	0.051	0.229	3.05	0.259	9.3	3.09	1.44	0.072	1.84
Si 3 m	0.040	0.242	0.479	0.070	0.245	0.87	0.036	0.202	3.17	0.271	8.4	4.21	1.09	0.058	1.87
C. Chronic thirst															
Sr 3 m	0.044	0.152	0.414	0.068	0.256	0.95	0.057	0.192	2.22	0.419	6.8	2.79	1.28	0.077	0.57
K 3.5 m	0.035	0.224	0.436	0.068	0.088	1.01	0.041	0.115	2.30	0,310	9.8	3.64	1.10	0.048	0.65
Sr 1 m	0.042	0.290	0.494	0.078	0.208	0.97	0.039	0.144	4.08	0.449	11.6	5.35	1.49	0.064	1.05
K 5.1 m	0.038	0.302	0.422	0.078	0.093	0.93	0.039	0.147	2.42	0.470	9.5	4.98	1.16		1.02
K 2.1 m	0.043	0.274	0.440	0.081	0.138	0.86	0.031	0.164	4.07	0.306	9.8	3.78	1.31		0.85
Si 4 m	0.039	0.300	0.463	0.055	0.157	0.98	0.065	0.191	4.14	0.390	9.7	3.95	1.20	0.048	1.04
Sr 2 m	0.041	0.296	0.410	0.073	0.232	0.91	0.054	0.196	3.93	0.444	9.2	4.20	1.47	0.050	1.35
D. Total inanition															
Si 2 m	0.041	0.269	0.487	0.050	0.237	0.092	0.052	0.179	3.39	0.383	6.6	4.90	1.30	0.060	1.47

TABLE 1—*Continued*

Individual data for controls and test rats in the various experiments. Weight in grams; lengths in mm.

RAT NUMBER AND SEX	EPIDIDYMIDES	THYROID	THYMUS	SUPRARENALS	HYPOPHYSIS
A. Controls					
K 3 m	0.701	0.0157	0.217	0.043	0.0057
K 3.1 m	0.911	0.0181	0.276	0.044	0.0063
Sr 6 m	0.807	0.0202	0.066	0.036	0.0061
Sr 7 f		0.0172	0.022	0.065	0.0126
B. Acute thirst					
K 4.1 m	0.456	0.0088	0.026	0.037	0.0059
K 3.4 m	0.558	0.0138	0.046	0.034	0.0047
Sr 8 m	0.676	0.0164	0.044	0.027	0.0062
Si 1 m	0.501	0.0129	0.056	0.027	0.0056
K 3.3 m	0.657	0.0202	0.052	0.038	0.0065
K 3.2 m	0.694	0.0156	0.085	0.028	0.0047
K 7.1 m	0.488	0.0117	0.007	0.036	0.0070
Si 3 m	0.487	0.0105	0.010	0.031	0.0066
C. Chronic thirst					
Sr 3 m	0.568	0.0131	0.016	0.025	0.0056
K 3.5 m	0.648	0.0073	0.015	0.030	0.0053
Sr 1 m	1.054	0.0115	0.015	0.032	0.0065
K 5.1 m	1.016	0.0110	0.018	0.036	0.0056
K 2.1 m	0.853	0.0107	0.009	0.025	0.0054
Si 4 m	1.038	0.0129	0.017	0.028	0.0071
Sr 2 m	1.351	0.0168	0.012	0.033	0.0072
D. Total inanition					
Si 2 m	0.356	0.0105		0.034	0.0065

During the experiment the rats were kept each in a separate cage with wire-net bottom. This allowed the feces and urine to drop through. Both feces and food were carefully weighed.

Acute thirst. Nine rats (eight included in table 1) were used for the acute-thirst experiment. They were allowed dry food ad libitum. The greatest difficulty in thirst experiments is to induce the animals to eat dry food. If they refuse to eat, the result is total inanition, instead of water inanition. The occurrence of partial inanition (due to deficiency in vitamines or other necessary dietetic elements) must also be avoided so far as possible. Various methods of feeding in the acute-thirst experiments (table 1) were used as follows:

Group 1. Two rats (K 4.1, K 3.4) were fed with maize (Indian corn) only, either whole grains or crushed, without water or milk. They consumed an average of about 1 gram daily. The feces averaged 2 to 2.7 grams daily.

Group 2. Two rats (Sr. 8, Si. 1) were fed with dry biscuit ad libitum and 3 grams of milk daily. Each rat daily ate 2.5 grams of biscuit and passed 2 grams of feces (average).

Group 3. Two rats (K 3.3, K 3.2) were fed with dry biscuit and 5 grams of milk daily. They daily ate 2.9 grams of dry biscuit and passed 0.8 gram of feces.

Group 4. In this group, two rats (K 7.1 and Si. 3) in the earlier days of the test were given (in addition to dry biscuit or maize and biscuit) relatively greater amounts of milk (15 to 20 grams), which was gradually reduced in the later days to 2 to 2.5 grams. By this method the rat ate relatively more food and continued active for a much longer period (killed after sixteen to seventeen days).

The daily average food intake for rat K 7.1 was 1.9 grams of biscuit and 6.3 grams of milk. The feces averaged 2.7 grams daily. For the other rat (Si. 3) the corresponding daily averages were 2 grams of biscuit and maize; 5.1 grams of milk; 0.4 gram of feces.

In addition to the groups above mentioned, a male rat (Si. 2) was kept alive without food or water (D; total inanition) for eleven days. This rat will be compared with those in the thirst series.

Chronic thirst. In the chronic-thirst experiments, seven rats were used. Six (table 1) were fed upon dry biscuit ad libitum with milk gradually decreased in amount, so as to reduce the body weight about 1 per cent (of the initial weight) daily. They were killed after an average of 50.6 (range 47 to 55) days (table 1). These rats daily ate an average of 6.9 grams of dry biscuit and 9 grams of milk. The feces averaged 1.1 grams daily. One rat (Sr. 3) ate a daily average of 6.7 grams of maize and 6.5 grams of whole milk. Another rat (Si. 4)was fed with dry biscuit and 6 grams of milk daily. This rat took an average of 6.3 grams of biscuit and passed an average of 1 gram of feces daily. In the rats of the acute-thirst series, it was observed that those getting 5 grams of milk a day (that is, only a little less than in the chronic series above) weakened rapidly and could live only about ten days. It therefore appears that, under the conditions stated, the water contained in about 6 grams of milk represents a critical limit, below which the rats can live but a few days.

In order to determine the amount of dry biscuit or corn required for maintenance, when water is allowed ad libitum, supplementary experiments were made upon adult rats. It was found that under these conditions about 13 to 15 grams of dry biscuit or maize are required to maintain approximately constant body weight for short periods. Jackson ('15) found that in adult rats with water ad libitum a diet of Graham bread soaked in whole milk and amounting to 10 per cent of the body weight daily is not quite sufficient for maintenance. It is therefore evident that in the present experiments the food-intake was not sufficient for maintenance, so that to some extent the effects of general inanition are added to those of thirst.

At the end of both acute and chronic thirst experiments, the rats were killed by chloroform and the various organs and parts carefully dissected and weighed. The technique followed is that described by Donaldson ('15), with a few modifications. The submaxillary glands and thyroid gland were removed first. The blood is so thick during thirst that slight pressure upon the body is necessary to obtain any appreciable flow even from the larger vessels. The organs and parts upon removal were placed in a closed jar upon glass plates resting on moist filter-paper.

The organs, after weighing, were dried to constant weight in an oven at about 95°C., in order to determine their water content (not included in this paper).

Percentage losses in the various organs were calculated as follows. The average weight (table 2) for each organ or part in the test rats was compared with the corresponding average for the controls. The data in the column 'Difference' express the apparent percentage change (+ or −) as the result of the experiment. In calculating these percentage changes the slight differences in average initial body weights between the controls and the test rats are ignored.

For various reasons, the data obtained do not justify any final conclusions as to the effects of thirst. The number of animals used (especially for controls) is comparatively small, and in some cases there are marked individual variations (due partly to unavoidable variations in technique), as shown in table 1. Moreover, it is obviously difficult to separate the effects of thirst from the accompanying inanition due to inadequate food-intake. By comparison of the results with those obtained by inanition with water or by total inanition, however, it is possible to reach some general conclusions of interest and importance.

GENERAL OBSERVATIONS

The symptoms noted in the albino rats during the thirst experiments are briefly as follows. The skin becomes roughened and the hairs are easily detached. (Likewise noted in dogs on a dry diet by Bowin, '80.) Dryness and desquamation were observed in the skin of the plantar surfaces. The fecal material is usually hard, but sometimes diarrheal in character. The urine is scanty. Opacity of the lens apparently caused visual disturbance in some cases. The conjunctiva was observed in some cases to be congested, and in one case hemorrhagic. Hemorrhage from the nose was noted in several cases. Paralysis of the right posterior extremity occurred in one case. During the period of twelve to twenty-four hours before death the rats will take neither food nor milk and are exhausted, apathetic, and convulsive. Some rats apparently become mentally deranged and will bite, although previously they were very tame. Mental disturbance has also been noted in men during extreme thirst (Tiedemann, '36; Zabaver, '04). The rat (Si. 2) subjected to total inanition ate about half of its tail during the experiment. In the chronic-thirst series, the rats always had the penis extruded, possibly from attempts to get the urine.

The general conditions observed at autopsy are as follows. There is extreme general emaciation. The skin and muscles appear dry and are difficult to separate. The blood is very thick. The fat has almost disappeared from the subcutaneous and muscular tissues, but persists in small amount in the orbit. The adipose tissue of the interscapular region is reduced to a small, brownish-red mass. A small amount of serous fluid is found in the peritoneal, pleural, and pericardial cavities. The appearances of the brain, spinal cord, lungs, and abdominal viscera will be mentioned later in discussing the individual organs.

BODY WEIGHT

As shown in tables 1 and 2, the average initial gross body weight of eight rats in the acute-thirst series is 218.8 grams and in the three controls, 218.3 grams. The loss in body weight in the acute-thirst series averages 36.1 per cent, the loss in individual cases ranging from 31.8 per cent to 45.9 per cent. This represents nearly the maximum possible loss during the acute-thirst experiments, as the rats were killed only in very advanced stages of inanition. Three other rats of 152, 162, and 208 grams that were fed small amounts of milk (average 3, 2, and 2.8 grams daily) died with losses in body weight of 33.8, 31.6, and 35.7 per cent, respectively. These rats have been excluded from the tables, as previously explained. In the rat (Si. 2) on total inanition, the body weight decreased from 216 grams to 114 grams, a loss of 47.2 per cent in eleven days, at the end of which time the rat was killed.

These losses in total and acute water inanition are greater than those obtained by Jackson ('15) in acute inanition with water. In a series of fifteen albino rats, he obtained an average loss of 33.1 per cent (range 25 to 40 per cent) in an average of nine (six to twelve) days.

In my chronic-thirst series the loss in body weight is remarkably greater than in acute thirst. The average body weight for the seven test rats (tables 1 and 2) shows a loss of 52.4 per cent (range, 50.6 to 60.2 per cent). The loss in body weight in this chronic-thirst series is also markedly greater than that obtained in albino rats in chronic inanition with water by Jackson ('15), which averaged 36.1 per cent (extreme 37.5 per cent) in five weeks. In a dog, given water only, Kumagawa ('98) observed a loss of 56 per cent in the body weight in ninety-eight days. As the result of a dry diet, Bowin ('80) obtained a loss of 50 per cent in the body weight of dogs and rabbits; Scheffer ('52) a loss of 45.8 per cent in pigeons; and Pernice and Scagliosi ('95) a loss up to 41.2 per cent in chickens. In rabbits, Skoritschenko ('83) noted very irregular losses in body and organ weights. In the acute thirst of experimental diarrhea, however, Tobler ('10) produced the death of dogs in three and one-half to seven days, with loss of only 22 to 30 per cent in body weight.

In the present experiments there is no constant relation between the percentage loss in body weight and either the initial body weight or the length of the thirst period. However, in each case the loss in body weight during acute thirst is greater during the first half than during the second half of the experiment. As might be expected, the loss during thirst is invariably the greatest on the first day, as found by numerous investigators in various animals and types of inanition. This is probably due chiefly to the reduction in contents of the stomach and intestines.

LENGTHS OF BODY AND TAIL

The body length is measured from the tip of the nose to the anus and the tail length from the anus to the tip of the tail. The measurements were taken immediately after death, the body and tail being extended by very slight tension.

The body length (table 1) in the acute-thirst series shows an average loss of 11.4 per cent and in the chronic-thirst series a loss of 14.7 per cent, in comparison with the controls. In the rat (Si. 2) on total inanition the corresponding apparent decrease is 12.5 per cent. This decrease in the trunk length, as noted by

Jackson ('15) in rats on water only, is probably due to shrinkage of the intervertebral disks. In the tail the shrinkage is evident, though less marked than in the body; thus the tail becomes relatively longer in the test rats.

WEIGHTS OF ORGANS AND SYSTEMS

Integument

As shown in table 2, the integument (which includes the skin appendages, external ear, hair, and claws) has in the acute-thirst series apparently decreased in absolute weight from an average of 41.9 grams to 28.5 grams, which is a loss of 31.9 per cent in average weight (table 2). In the chronic-thirst series, the corresponding decrease is from 40.2 grams to 21.3 grams, a loss of 47 per cent. In the rat (Si. 2) on total inanition (table 1) the apparent loss in weight of the integument amounts to 42.5 per cent.

Since these losses are only slightly less than those of the whole body, there is but little change in the relative weight of the integument. Jackson ('15) also found that in rats after inanition with water the loss of weight in the integument is nearly proportional to that of the entire body. (Scheffer, '52, and Falck and Scheffer, '54, in the dog on dry diet, found the loss in the body weight (20.7 per cent) somewhat less than that in the integument (25 to 28 per cent.)

Skeleton

The skeleton (tables 1 and 2) was prepared in two ways. According to Jackson ('15), the bones, together with the cartilages, periosteum, and ligaments, constitute the 'ligamentous skeleton.' The bones and cartilages, after removal of the periosteum and ligaments by immersion for about one hour in 1 per cent of solution of 'gold dust' (a soap mixture) at 90°C., constitute the 'cartilaginous skeleton.' The humerus and femur were also weighed fresh, after removal of the periosteum and ligaments, to avoid possible effects of heating in the soap solution.

As shown in table 2, the ligamentous skeleton of the acute-thirst series shows a loss of 4.3 per cent in average weight, and during the chronic-thirst series a loss of 10.3 per cent. Since the corresponding loss in the body weight is much greater, the skeleton increased correspondingly in relative weight during the experiments.

The cartilaginous skeleton similarly shows a loss in average weight of 11.8 per cent in the acute-thirst series and 5 per cent in the chronic-thirst series. (The apparent loss of 34.1 per cent in the skeleton of rat Si. 2, on total inanition (table 1), is due to an error in technique.)

The data for the humerus (2) and femur (2) show a loss in average weight of 21.1 per cent in the acute-thirst series and 12.1 per cent in the chronic-thirst series. This indicates that the loss in these large bones is relatively greater than in the remainder of the skeleton.

Jackson ('15) found that in albino rats during acute and chronic inanition (with water) there is apparently little or no loss of weight in the skeleton, and cited numerous data showing similar results by other investigators in various species.

Falck and Scheffer ('54), in a dog on dry diet, found a loss of 20.7 per cent in body weight and a loss of 5.3 per cent in the ligamentous skeleton. In the acute thirst, caused by experimental diarrhea in dogs, Tobler ('10) found a loss of 4 to 15 per cent in the weight of the (cartilaginous?) skeleton. Thus it is evident that during inanition, either with or without water, the skeleton decreases but slightly in weight.

Musculature

The musculature in the acute-thirst series shows a loss in average weight of 33.1 per cent and in the chronic-thirst series a loss of 61.2 per cent (table 2).

The corresponding percentage losses in body weight and in musculature found by previous observers as a result of thirst are as follows: in the pigeon (Schuchardt, '47), body −43.9, musculature −37; in the dog (Falck and Scheffer, '54), body −20.7, musculature −29.3.

During inanition with water, Jackson ('15) observed the following percentage losses in body weight and weight of musculature, respectively: acute inanition, body −33.9, musculature −30.9; chronic inanition, body −36.1, musculature −40.8. Results of other investigators cited by Jackson support the conclusion that in general the loss of weight in the musculature during inanition is roughly proportional to the loss in body weight, with a tendency to relatively greater loss during chronic inanition. This is in general agreement with the results of thirst, as above given.

Viscera and 'remainder'

In the visceral group (tables 1 and 2) have been included the brain, spinal cord, hypophysis, eyeballs, parotid, and submaxillary glands, as well as the thoracic and abdominal viscera. The visceral group in the acute-thirst series shows a loss of 30.6 per cent in average weight and in the chronic-thirst series 42.2 per cent. This is relatively somewhat less than the corresponding loss in body weight. Thus the relative (percentage) weight of the visceral group is not much changed, although (as will appear later) there is great variation in this respect among the individual organs.

The 'remainder' includes that which remains after dissecting from the rat body the skin, skeleton, musculature, and the visceral group mentioned above. It does not include the escaped blood and other fluids. It includes the dissectable fat tissue, mesentery, some nerves and vessels, a few small unweighed organs, and lymphatic glands. The latter were apparently enlarged in some of the test rats.

The 'remainder' shows a loss of 72.7 per cent in average weight in the acute-thirst series and of 88.8 per cent in the chronic series. In the rat (Si. 2) on total inanition (table 1) the corresponding loss in the 'remainder' amounts to 77.8 per cent. This loss is undoubtedly due chiefly to the loss of fat, which has almost disappeared in the test rats.

Brain

The brain in some cases appeared markedly congested at autopsy. In the acute-thirst series the brain apparently remains nearly constant in average weight with an insignificant increase of 0.12 per cent (table 2). In the chronic-thirst series the average brain weight lost 4.2 per cent. The ininvidual variations are small (table 1). In the rat (Si. 2) on total inanition the corresponding apparent loss in the weight of the brain is 7.6 per cent. The mean brain weight for the controls was about 7 per cent below the table value for rats of this length (Donaldson, '15).

The data available in the literature concerning the effects of thirst on brain weight are somewhat contradictory. Falck and Scheffer ('54) in a dog losing 20.7 per cent in body weight, noted an apparent gain of 7.2 per cent in brain weight. Bowin ('80) in rabbits on dry food with 50 per cent loss in body weight, noted an absolute decrease (but relative increase; amounts not stated) in the brain weight. Tobler ('10), in three dogs after experimental diarrhea with loss of 22 to 30 per cent in body weight, observed an apparent gain of 4.2 to 13.7 per cent in brain weight. The increase in weight might perhaps be due partly to the congestion or to individual differences between the test animals and the controls.

As to the effects of ordinary inanition, it has long been known that of all of the organs, the central nervous system is one of the most resistant to changes in weight. Jackson ('15) found an apparent loss of only 5 or 6 per cent in the brain of rats subjected to acute or chronic inanition (with water) and cites from the literature numerous data indicating little or no change in brain weight in other animals. On the whole, it appears evident that, during thirst, both acute and chronic, as well as during ordinary acute and chronic inanition with or without water, there is but little change (usually a slight decrease) in the weight of the brain. McCarrison ('19), as an effect of vitamine-deficient diets, finds an apparent slight decrease in the brain weight of pigeons, but an increase (average 1/7) in monkeys.

Spinal cord

The spinal cord, like the brain, sometimes appeared definitely congested at autopsy. In the acute-thirst series the spinal cord shows an apparent increase of 1.8 per cent in average weight, and in the chronic-thirst series a loss of 6.7 per cent (table 2). It is evident that in the spinal cord, as in the brain, there is no appreciable change in weight during acute thirst and a slight loss during chronic thirst. The apparent loss of 16.7 per cent in the spinal cord of the rat (Si. 2) on total inanition (table 1) is probably due to an individual variation. Falck and Scheffer ('54) observed an apparent loss of 7.1 per cent in the weight of the spinal cord of a dog kept on dry diet with a loss of 20.7 per cent in body weight.

Likewise in albino rats after inanition with water, Jackson ('15) noted no significant change in the weight of the spinal cord during acute inanition and a loss of but 4 per cent during chronic inanition. He cited observations of several previous investigators who obtained similar results in various animals during inanition with or without water.

Sciatic nerves

In order to study the effects of thirst upon the weight of the peripheral nerves, sciatic nerves (nn. ischiadici) on both sides were cut proximally at the exit from the pelvic cavity in the thigh and distally at the middle of the thigh. As seen in table 1, the data show considerable individual variation, so no stress can be laid upon differences between the results. In the acute-thirst series (table 2) the nerves show an apparent loss of 21.3 per cent in average weight, and in the chronic-thirst series a loss of 22.1 per cent. This would indicate that during thirst the loss in weight is relatively greater in the peripheral than in the central nervous system. No observations by others upon this point have been found in the literature, but Doctor Hatai has called my attention to the fact that there is a large amount of fat usually present in the normal sciatic nerve.

Eyeballs

The occurrence of conjunctival congestion (or hemorrhage) and the opacity of the lens were mentioned under 'General observations.' Conjunctival congestion during extreme human thirst was noted by Tiedemann ('36) and conjunctival infection was reported in the dog by Pernice and Scagliosi ('95). Opacity of the lens in dehydrated frogs was noted in some cases by Durig ('01).

As shown in table 2, the eyeballs in my acute-thirst series lose 10.2 per cent in average weight, and in the chronic-thirst series 13.3 per cent. In the rat (Si. 2), on total inanition, the apparent loss of weight in the eyeballs is 13 per cent. In a dog on dry diet with loss of 20.7 per cent in body weight, Falck and Scheffer ('54), on the contrary, found an apparent gain of 19.7 per cent (probably due to an individual variation) in the weight of the eyeballs. During inanition with water in the albino rat, no significant change in the weight of the eyeballs was found by Jackson ('15), who cites a few similar observations by previous authors. Bitsch ('95) found the absolute weight of the eyeballs in the dog usually increased during inanition, and suggested that it might be due to edema. Possibly the lack of available water during thirst may explain the decrease in the weight of the eyeballs in the present experiments, but a further investigation on this point is required before a final conclusion can be reached.

Heart and aorta

Heart. The heart in the acute-thirst series (table 2) shows a loss of 30.6 per cent in average weight, and in the chronic-thirst series a loss of 46.3 per cent. In the rat (Si. 2), after total inanition (table 1), the corresponding apparent loss is 42.6 per cent. Since the heart during thirst loses somewhat less in weight than does the body as a whole, it increases accordingly in relative (percentage) weight.

Few data in the literature are found concerning the weight of the heart during thirst. Falck and Scheffer ('54) noted in the dog a loss of 4 per cent in the heart and aorta, with a loss of 20.7

per cent in body weight. Bowin ('80) also noted in rabbits an absolute decrease (but relative increase) of weight in the heart during thirst. Tobler ('10) obtained variable results (+4.1 to −21.5 per cent) in the weight of heart and lungs together in dogs subjected to experimental diarrhea with loss of 22.4 to 29.8 per cent in body weight.

After inanition of albino rats with water, Jackson ('15) likewise noted that the loss of weight in the heart is somewhat less than that in the body as a whole. He cites data from several previous observers showing similar results in various animals. An atrophy of the heart in pigeons and monkeys on vitamine-deficient diets has recently been observed by McCarrison ('19).

Aorta. The aorta was cut anteriorly at its junction with the heart and posteriorly at its bifurcation. All the branches of the aorta were clipped close to the vessel, and the surrounding fat tissue and lymphatic nodules were removed. The blood was removed from the aorta, and the vessel was weighed in two controls, two test rats in acute-thirst, and seven in chronic-thirst experiments (table 1).

The aorta in the acute-thirst rats apparently decreased in average weight 42.5 per cent and in the chronic-thirst 44.6 per cent. While the number of observations (in the controls and the chronic tests) is too small to be very significant, the results indicate that the loss in the weight of the peripheral arteries may be fully as great as that of the heart.

Spleen

The spleen at autopsy usually appeared small and atrophic. The capsule is sometimes thickened. Upon section, the pulp appeared relatively pale brownish, and the trabeculae more prominent than in the normal organ. The spleen in the acute-thirst series (table 2) shows a loss of 66 per cent in average weight and in the chronic-thirst series a loss of 73.3 per cent. In the rat (Si. 2), after total inanition, the corresponding apparent loss in the weight of the spleen is 62.9 per cent. As seen from table 1, the weight of the spleen, even in normal rats, is exceedingly variable. And yet the atrophy in both acute and chronic tests is so profound that the results are unquestionable.

Of previous investigators, only Falck and Scheffer ('54) record an apparent increase of 9 per cent in the weight of the spleen in a dog on dry diet (loss in body weight, 20.7 per cent). Bowin ('80) found a decrease in both absolute and relative weight of the spleen in dogs and rabbits with loss of about 50 per cent in body weight. In three dogs, after experimental diarrhea (with loss of 22.4 to 29.8 per cent in body weight), Tobler ('10) found a loss of 32.5 to 75.9 per cent in the weight of the spleen.

In albino rats, after inanition with water, Jackson ('15) noted an average loss of 51 per cent in the spleen in the acute series (body weight, −33.9 per cent) and of 29 per cent in the chronic series, (body weight, −31.1 per cent). He cites similar results by numerous observers in man and various animals subjected to inanition with or without water. It thus appears that profound atrophy of the spleen is not characteristic of thirst, but usually appears also in inanition with or without water. As an effect of vitamine-deficient diets, a marked atrophy of the spleen has been observed by McCarrison ('19) in pigeons, and a less marked atrophy in monkeys.

Lungs

The characteristic pathological changes due to lung infection were rarely observed in my test rats, although slight infection is probably responsible in part for the abnormally high weight in the controls (table 1). The average weights (table 2) show an apparent loss of 44 per cent in the weight of the lungs in the acute-thirst series, and of 51.5 per cent in the chronic-thirst series. In the rat (Si. 2) after total inanition the corresponding apparent loss is 52.7 per cent. If, however, the normal weight of the lungs given by Donaldson ('15) be taken for comparison, the loss of weight in the lungs of the test rats would be only about 16 and 22 per cent, respectively, in the acute- and chronic-thirst series.

Of previous observers on the effects of thirst, Falck and Scheffer ('54) noted an apparent loss of 26.9 per cent in the weight of lungs, trachea, and pharynx, in a dog on dry diet with loss of 20.7 per cent in body weight. Bowin ('80) concluded that the changes in the weight of the lungs in dogs and rabbits on dry diet are the same as during total inanition.

In rats after inanition with water, Jackson ('15) found an apparent loss of 30.9 per cent in the lungs of the acute series and 40 per cent in the chronic series, which was roughly proportional to the loss in body weight. He cites previous observations by others indicating that the loss in weight of the lungs during inanition (with or without water) is usually less than that of the body. McCarrison ('19) has likewise noted a decrease in the weight of the lungs in monkeys on vitamine-deficient diets.

Parotid and submaxillary glands

The parotid glands are easily removed and separated from the adjacent lymphatic nodules and facial nerve. The submaxillary glands were similarly isolated. The adjacent lymphatic glands sometimes appeared enlarged in the test rats, in contrast with the salivary glands. The weights of the submaxillary glands in the controls were a little heavier than those given by Hatai ('18).

The parotid glands in the acute-thirst series show a loss of 57.6 per cent in average weight (table 2) and in the chronic-thirst series a loss of 69.7 per cent. In the rat (Si. 2) on total inanition (table 1) the apparent loss in the weight of the parotid glands is 67.7 per cent. The submaxillary glands similarly lose 47.1 per cent in average weight in the acute-thirst series, and 64.5 per cent in the chronic-thirst series. In the rat (Si. 2), after total inanition, the apparent loss in weight of the submaxillary glands is 63.3 per cent.

Thus the salivary glands during thirst and after total inanition evidently undergo a profound atrophy, decreasing in weight relatively more than the body as a whole. Falck and Scheffer ('54) similarly found a loss of 33.7 per cent in the weight of the salivary glands in a dog on dry diet with loss of 20.7 per cent in body weight. McCarrison ('19) finds an atrophy of the submaxillary glands in monkeys on vitamine-deficient diets.

Liver

At autopsy, the liver usually appears somewhat hyperemic, the capsule being normal. In the acute-thirst series (table 2) the liver shows a loss of 37 per cent in average weight and in the chronic-thirst series a loss of 55.3 per cent. In the rat (Si. 2) after total inanition (table 1) the apparent loss in weight of the liver is 53 per cent. Thus it is evident that the liver during thirst has lost weight in nearly the same proportion as the whole body, but relatively more in the chronic-thirst series and during total inanition.

Of other investigators on the effects of thirst, Falck and Scheffer ('54) found a loss of 25.3 per cent in the liver weight (body weight, −20.7 per cent). In dogs and rabbits with loss of 50 per cent in body weight, Bowin ('80) found the loss in liver weight similar to that during total inanition. Finally, in three dogs after experimental diarrhea with loss in body weight of 22.7 to 29.8 per cent, Tobler ('10) noted a loss of 17.9 to 34.8 per cent in the weight of the liver.

In albino rats subjected to inanition with water, Jackson ('15) obtained a loss of 58 per cent in the acute tests (body weight, −33.9 per cent) and of 43 per cent in the chronic tests (body weight, −36.1 per cent). He cites numerous data from previous observers indicating that in man and other species the liver invariably decreases markedly in weight during inanition (with or without water). The loss is nearly always relatively greater than that of the body as a whole. Lasarew ('95) found that the loss in the weight of the liver in the guinea-pig is relatively greater during the earlier stages of inanition. McCarrison ('19) finds an atrophy of the liver of pigeons and monkeys on vitamine-deficient diets.

Pancreas

The pancreas, especially in the case of the thirst experiments, appears atrophic and is rather difficult to dissect out from the surrounding adipose tissue, omentum, and lymphatic glands. The pancreas in the acute-thirst series shows a loss of 53.1 per cent in average weight (table 2), and in the chronic-thirst series a loss of 52.7 per cent. In the rat (Si. 2), after total inanition, the corresponding apparent loss in weight of the pancreas (table 1) is 58.6 per cent. Thus the relative loss appears to be similar to that in the combined salivary glands, though somewhat less during chronic inanition.

In a dog on dry diet with loss of 20.7 per cent in body weight, Falck and Scheffer ('54) found a loss of 36.1 per cent in the weight of the pancreas. Similarly, Lukjanow ('89) observed a loss of 54.4 per cent in the weight of the pancreas (body weight, −34 per cent) in pigeons after total inanition. These results are in fair agreement with my observations on rats. Atrophy of the pancreas was also observed by McCarrison ('19) in pigeons and monkeys on vitamine-deficient diets.

Stomach and intestines

In two cases of acute thirst ulceration and hemorrhage of the stomach were observed in the mucosa near the cardia. The digestive tube, from the level of the diaphragm to the anus, was removed and separated from the pancreas, mesentery, etc., and weighed with and without contents.

The stomach and intestines, including their contents in acute thirst, show an apparent loss of 36.4 per cent in average weight, and in chronic thirst a loss of 28.3 per cent (table 2). In the rat (Si. 2) after total inanition (table 1) the apparent loss is greater, amounting to 52.1 per cent.

The stomach and intestines, without contents, in the acute-thirst series show a loss of 29.1 per cent in average weight, and in the chronic-thirst series a loss of 31.8 per cent (table 2). In the rat (Si. 2) after total inanition (table 1) the corresponding apparent loss is 20.3 per cent. In all cases the loss is relatively less in the stomach and intestines than in the body as a whole.

In a dog on dry diet with loss of 20.7 per cent in body weight, Falck and Scheffer ('54) noted an apparent loss of 7.6 per cent in the weight of the stomach and of 17.9 per cent in that of the intestines. In three dogs after experimental diarrhea with loss of 22 to 30 per cent in body weight, Tobler ('10) found apparent losses of 2.5 to 34.5 per cent in the weight of intestinal tract.

Following the inanition of albino rats with water, Jackson ('15) found a loss of 57 per cent in the gastro-intestinal tract of both the acute- and chronic-inanition series (body weight loss 33.9 and 36.1 per cent). He cites previous observations by Sedlmair ('99), indicating in the cat during inanition a loss in the intestinal tract proportional to that in body weight, and a relatively smaller loss observed by Voit ('66). McCarrison ('19) finds marked inflammatory changes with degenerative atrophy of the gastric and intestinal mucosa in pigeons, guinea-pigs, and monkeys on vitamine-deficient diets.

Kidneys and bladder

Kidneys. At autopsy the kidneys usually appear hyperemic. In a few cases the surface was roughened. The capsule is easily removed. The kidneys in the acute-thirst series (table 2) show a loss of 23.8 per cent in average weight and in the chronic-thirst series a loss of 31.4 per cent. In the rat (Si. 2) after total inanition (table 1) the apparent loss in the weight of the kidneys is 30.5 per cent. In all of these it appears that the kidneys lose in weight relatively less than the body as a whole, thus gaining in relative (percentage) weight.

In thirst experiments on the dog, Falck and Scheffer ('54) likewise found the loss in the kidneys and ureters (−8.7 per cent) less than in the whole body (−20.7 per cent). Tobler ('10) found in three dogs after experimental diarrhea a loss of 5.64, to 30.1 per cent in kidney weight (body weight loss 22 to 30 per cent). Durig ('01), however, in dehydrated frogs found a relative increase in the weight of the kidneys.

In rats after inanition with water, Jackson ('15) found a loss of 25.5 per cent in the acute series (body weight, −33.9 per cent) and of 26.8 per cent in the chronic series (body weight, −36.1 per cent). He cites results from previous observers likewise indicating for other animals (in most cases) a loss in kidney weight relatively less than in body weight in inanition with or without water. McCarrison ('19) likewise finds an atrophy of the kidneys in pigeons and monkeys on vitamine-free diets.

Bladder. The urinary bladder was isolated from the surrounding adipose tissue and peritoneum. At autopsy the bladder is always empty and contracted; its mucosa appeared hyperemic. Unfortunately, the weights were recorded in only a few cases (table 1). The bladder in the test animals (table 2) shows in average weight an apparent loss of 39.7 per cent in the acute-thirst series and of 46.9 per cent in the chronic-thirst series. Although the observations are too few for definite conclusions, it appears that the loss of weight in the bladder is relatively greater than in the kidney, and is more nearly proportional to that of the body as a whole. Falck and Scheffer ('54) in a dog on a dry diet found an apparent loss of 34.9 per cent in the weight of the bladder (body weight, −20.4 per cent).

Testes

The testes during thirst, especially in the chronic-thirst series, appear atrophic and often become softer than in the controls. The test rats show no spermatozoa in the ductus deferens or seminal vesicles.

In the acute-thirst series the testes apparently lose only 15.1 per cent in average weight, but in the chronic-thirst series the loss is 59.9 per cent (table 2). In the rat (Si. 2) after total inanition (table 1) the corresponding apparent loss is 36.9 per cent. In a dog on dry diet, Falck and Scheffer noted an apparent loss of 23.5 per cent in the weight of the testes and penis (body weight, −20.7 per cent).

In albino rats after inanition with water, Jackson ('15) found the loss in weight of the testes is, relatively, slightly less than that of the body as a whole during acute inanition, and slightly greater than that during chronic inanition. In the cat a relative decrease in the weight of the testis during inanition was observed by Voit ('66). McCarrison ('19) finds a marked atrophy of the testis in pigeons on vitamine-free diets and a less marked atrophy in monkeys.

Epididymis

The epididymis in the acute-thirst series (table 2) shows a loss of 30 per cent in average weight and in the chronic-thirst series a loss of 64.8 per cent. In the rat (Si. 2) after total inanition (table 1), the corresponding apparent loss in weight of the epididymis is 55.8 per cent. In all cases, therefore, the loss appears slightly greater (relatively) in the epididymis than in the testis. Jackson ('15) concluded that in the albino rat after inanition with water the loss in weight of the epididymis is relatively not very different from that in the testis.

Thyroid gland

The thyroid gland in the acute-thirst series undergoes a loss of 23.9 per cent in average weight, and in the chronic-thirst series a loss of 33.1 per cent. In the rat (Si. 2), after total inanition (table 1), the apparent loss in weight of the thyroid is 41.7 per cent. In a dog on a dry diet, Falck and Scheffer ('54) noted an apparent loss of 30 per cent in the weight of the thyroid (body weight, −20.7 per cent). In acute inanition with water, Jackson ('15) found in the thyroid of the albino rat a loss in weight proportional to that of the whole body (about 34 per cent), and during chronic inanition with water a loss of 21.8 per cent (body weight, −36.1 per cent). The extent of the loss in weight of the thyroid during inanition appears quite variable, due in part to the difficulty in dissecting out the gland uniformly. McCarrison ('19) noted a slight atrophy of the thyroid in pigeons and monkeys on vitamine-free diets.

Thymus

In the acute-thirst series the thymus (table 2) shows an apparent loss of 78.1 per cent in average weight and in the chronic-thirst series a loss of 90 per cent. There is some uncertainty about these conclusions, however, as the age of the rats is unknown in some cases. It has been shown (Jackson, '13; Hatai, '14) that the thymus in the rat normally undergoes an age involution, and the smaller weight of the thymus in the test rats may be partly due to their greater age. The weight of the thymus in the test rats is far below the normal for the corresponding age, however.

In a dog on dry diet, Falck and Scheffer ('54) observed an apparent loss of 63.1 per cent (body weight, −20.7 per cent). Hammar ('06) has shown the general occurrence of hunger involution of the thymus during inanition, which has been thoroughly investigated in the rabbit by Jonson ('09). McCarrison ('19) has likewise noted a very great atrophy of the thymus in pigeons and monkeys on vitamine-deficient diets.

Suprarenal glands

Since the suprarenal glands normally show a sexual difference in weight from the age of about six weeks, the sexes must be considered separately. In the following discussion, the data concern only the males.

In the acute-thirst series the suprarenal glands show a loss of 21.3 per cent in average weight (table 2), while in the chronic-thirst series there is an apparent loss of 27.1 per cent. In the latter case, the initial body weight of the (three) male controls is about 3 per cent greater than that of the test rats, so there is definite loss in the weight of the suprarenals during the thirst experiments. In the rat (Si. 2) after total inanition (table 1), the apparent decrease in weight of the suprarenals amounts to 16.6 per cent.

No data were found in the literature concerning the weight of the suprarenal glands during thirst. During inanition of albino rats with water, Jackson ('15) found in the acute-inanition series an apparent increase of 1.5 per cent in weight and in the chronic-inanition series a decrease of 8.9 per cent (loss in body weight, 33.9 and 36.1 per cent, respectively). It therefore appears that during inanition with water the suprarenal glands are more resistant to changes in weight than they are during thirst and total inanition. In pigeons, guinea-pigs, and rabbits on vitamine-deficient diets, McCarrison ('19) finds a definite increase in the weight of the suprarenals. In scorbutic guinea-pigs he finds the weight, even doubled, but associated with degenerative changes.

Hypophysis

In the case of the hypophysis, as with the suprarenal glands, there is normally a sexual difference in weight (Hatai, '13). Males only are considered in the following discussion.

The hypophysis in the acute-thirst series shows an apparent loss of 1.7 per cent (in an average weight) and in the chronic-thirst series a gain of 1.7 per cent. These differences are too small to be considered significant. The apparent increase of 8.3 per cent in the weight of the hypophysis in rat Si. 2 (table 1) on total inanition is perhaps due to an individual variation.

No data have been found in the literature concerning the changes of weight in the hypophysis during thirst. In albino rats after inanition, with water, Jackson ('15) found the weight of the hypophysis apparently decreased relatively slightly less than the whole body. It would therefore appear that during inanition with water there is a marked loss in the weight of the hypophysis, whereas during the thirst experiments and total inanition it remains more nearly constant. McCarrison ('19) finds as result of vitamine-deficient diets the hypophysis (glandular lobe) slightly increased in pigeons, and usually so in monkeys.

DISCUSSION

The changes in the absolute weights of the various systems and organs as a result of thirst in the adult albino rats are summarized in table 2. While (as previously stated) no great emphasis can be laid upon the exact values, it is apparent that, with reference to the relative loss in weight during the thirst experiments, the various organs and systems may be divided into three groups.

In the first group, the loss of the organs in weight is relatively greater than that for the whole body. In the second, the loss is less than that for the entire body—but more than half as great—and finally in the third group it is less than half that for

TABLE 2

Average weights for controls and test rats in the thirst experiments, with percentage difference. Data from table 1

	ACUTE THIRST: 6 TO 16 DAYS			CHRONIC THIRST: 47 TO 55 DAYS		
	Average weight in		Difference	Average weight in		Difference
	Controls (3 males)	Test rats (8 males)		Controls (3 m., 1 f.)	Test rats (7 males)	
	grams	*grams*	*per cent*	*grams*	*grams*	*per cent*
Initial gross body weight	218.3	218.8	+0.2	211.8	211.3	−0.2
Final gross body weight	218.3	139.6	−36.1	211.8	100.9	−52.4
Integument	41.93	28.54	−31.9	40.15	21.27	−47.0
Ligamentous skeleton	20.24	19.36	−4.3	20.07	18.00	−10.3
Cartilaginous skeleton	16.34	14.41	−11.8	15.22	14.46	−5.0
Humerus (2) and femur (2)	2.08	1.64	−21.1	1.95	1.62	−12.1
Musculature	88.7	59.3	−33.1	86.6	33.6	−61.2
Visceral group	26.2	18.2	−30.6	25.4	14.6	−42.2
'Remainder'	15.15	4.14	−72.7	15.72	1.76	−88.8
Brain	1.766	1.768	+0.12	1.742	1.668	−4.2
Spinal cord	0.520	0.529	+1.8	0.546	0.509	−6.7
Sciatic nerves	0.055	0.043	−21.3	0.052	0.040	−22.1
Eyeballs	0.303	0.272	−10.2	0.303	0.263	−13.3
Heart	0.848	0.589	−30.6	0.819	0.440	−46.3
Aorta[1]	0.129	0.074	−42.5	0.129	0.072	−44.6
Spleen	0.638	0.217	−66.0	0.627	0.167	−73.3
Lungs	1.94	1.09	−44.0	1.94	0.94	−51.5
Parotid glands	0.160	0.068	−57.6	0.154	0.047	−69.7
Submaxillary glands	0.489	0.258	−47.1	0.462	0.164	−64.5
Liver	7.21	4.54	−37.0	7.40	3.31	−55.3
Pancreas	0.93	0.43	−53.1	0.84	0.40	−52.7
Stomach-intestines (filled)	13.78	8.77	−36.4	13.23	9.49	−28.3
Stomach-intestines (empty)	6.15	4.36	−29.1	6.01	4.10	−31.8
Kidneys	1.87	1.43	−23.8	1.89	1.29	−31.4
Bladder[1]	0.109	0.065	−39.7	0.109	0.058	−46.9
Testes[1]	2.33	1.98	−15.1	2.33	0.93	−59.9
Epididymides[1]	0.806	0.565	−30.0	0.806	0.283	−64.8
Thyroid	0.0180	0.0137	−23.9	0.0178	0.0119	−33.1
Thymus	0.187	0.041	−78.1	0.145	0.015	−90.0
Suprarenals[1]	0.0409	0.0322	−21.3	0.0409	0.0298	−27.1
Hypophysis[1]	0.0060	0.0059	−1.7	0.0060	0.0061	+1.7

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[1] In these cases the number of observations does not include all the members of the group, as explained in the text (table 1).

the entire body. In three organs in this last group there is apparently a slight gain. To make the comparison of the results in this manner, the data have been arranged as in table 3.

In addition to the organs listed in table 3, the few observations on the bladder and aorta (table 2) during thirst, both acute and chronic, indicate that these organs suffer a marked loss in weight.

If we compare the changes in weight of the organs or systems during acute thirst with those during chronic thirst, it appears that they are, on the whole, very similar, making due allowance for the greater loss of body weight in the chronic-thirst series. In a few organs, however, there is a considerable difference. For example, the testis, epididymis, and musculature suffer relatively a much heavier loss in weight in the chronic-thirst series than in the acute-thirst series.

On the whole, however, it is evident that the results in the two series are remarkably similar to each other, and also (especially the chronic series) to those obtained in the rat after total inanition.

A further study of the data for the acute-thirst series (tables 2 and 3) shows that the large losses in weight are suffered by 'the remainder' (composed mainly of fat, lymphatic glands, etc.), the integument (carrying fat), the visceral group (highly cellular), and the musculature, parts which taken together represent about 80 per cent of the gross weight of the control rats. It is evident from this that variations in the loss of other parts or organs will modify but slightly the total losses observed.

Comparing my results on thirst with the changes in weight of organs and systems of the albino rat found by Jackson ('15) during inanition with water, there appears a surprising degree of similarity. There are, of course, some organs which are more or less different. For instance, the thyroid gland, suprarenals, and intestinal tract apparently suffer a greater loss during thirst than during inanition with water; but it is somewhat doubtful whether the difference is due entirely to the difference in diet. The changes in the chronic series, either on a dry diet or with water, might possibly be due in part to lack of vitamines in the diet; but this could hardly be the case in the acute series, where the

TABLE 3

Based on table 2 and on table 1—for complete inanition. The percentage losses are given in three groups and in a regularly descending order for the series subjected to acute thirst. In the series for chronic thirst, and in the one rat after complete inanition, the losses are entered in the same order as in the acute-thirst series. In the last two series the values do not decrease regularly, but the arrangement facilitates comparison between the several series

	ACUTE THIRST	CHRONIC THIRST	COMPLETE INANITION
Organs showing a loss in weight greater than that of the entire body			
	per cent	*per cent*	*per cent*
Loss of weight for entire body	36.1	52.4	47.2
Organ or part			
Thymus	−78.1	−90.0	
Remainder	−72.7	−88.8	−77.8
Spleen	−66.0	−73.3	−62.9
Parotid glands	−57.6	−69.7	−67.6
Pancreas	−53.1	−52.7	−58.6
Submaxillary glands	−47.1	−64.5	−63.3
Lungs	−44.0	−51.5	−52.7
Liver	−37.0	−55.3	−53.0
Stomach and intestines (filled)	−36.4	−28.3	−52.4
Organs showing a percentage loss in weight less than that for the entire body—but more than half as great			
Organ or part			
Musculature	−33.1	−61.2	−39.2
Integument	−31.9	−47.0	−42.5
Heart	−30.6	−46.3	−42.6
Visceral group	−30.6	−42.2	−38.7
Epididymides	−30.0	−64.8	−55.8
Stomach and intestines (empty)	−29.1	−31.8	−20.3
Thyroid	−23.9	−33.1	−41.7
Kidneys	−23.8	−31.4	−30.5
Suprarenals	−21.3	−27.1	−16.6
Humerus Femur	−21.1	−12.1	
Organs showing a percentage loss in weight less than half that for the entire body			
Organ or part			
Testes	−15.1	−59.9	−36.9
Cartilaginous skeleton	−11.8	− 5.0	−34.1
Eyeballs	−10.2	−13.3	−13.0
Ligamentous skeleton	−4.3	−10.3	
Hypophysis	−1.7	+1.7	+8.3
Brain	+0.12	−4.2	−7.6
Spinal cord	+1.80	−6.7	−16.7

resulting changes in organ weights are in general very similar, although the experiments lasted but a few days. The extensive investigations of McCarrison ('19), however, have shown that in animals (pigeon, guinea-pig, monkey) on vitamine-deficient diets the various organs present atrophic changes, which resemble and are in some way related to those occurring in ordinary inanition.

The evident fact that the changes in organ weights in the present thirst experiments are in general very similar to those found during total inanition and in partial inanition of various kinds, may perhaps be explained in one of two ways. Either the effects of thirst closely resemble those of general inanition (perhaps in some way interfering with the normal process of metabolism) or they are masked and overshadowed to a large extent by the inanition which necessarily accompanies the thirst experiments, due to the inadequate food-intake. Further research will be necessary before this problem can be solved.

SUMMARY

The more important results of the present investigation may be summarized briefly as follows:

In the acute-thirst experiments, lasting from six to sixteen days, the amount of water in the diet was greatly reduced in eight test rats, resulting in a loss of 36.1 per cent in the average gross body weight in a few days. The corresponding percentage changes in the organs are most readily seen in table 3.

In the chronic-thirst experiments, lasting from forty-seven to fifty-five days, the amount of water in the diet was not so greatly reduced, resulting in a more gradual but greater loss of body weight, the loss in average weight of seven test rats being 52.4 per cent in about seven weeks. The corresponding percentage changes in the various parts are most readily seen in table 3.

In a single rat, after total inanition, the loss in body weight was 47.2 per cent in eleven days. The apparent loss in the individual parts is very similar to that during thirst (especially the chronic) series (table 3), making due allowance for the difference in the loss in body weight and the probability of individual variation in a single specimen.

The striking similarity in the changes in organ weights produced in the thirst and total inanition experiments is confirmed by the data from previous investigators as to the effects of total and partial inanition, with or without water, in the rat and other animals. It is yet uncertain whether this is because the primary effect of thirst is the same as that of other forms of inanition or whether the thirst effects are largely obscured by the accompanying inanition due to inadequate food intake.

LITERATURE CITED

BITSCH 1895 Pathologisch-anatomische Veränderungen der Netzhaut des Hundes beim Hungern. Dissertation, St. Petersburg. (Cited by Mühlmann, '99.)

BOWIN, M. 1880 Beiträge zur Frage über die Trockenernährung. Dissertation, St. Petersburg. (Cited by Mühlmann, '99.)

DONALDSON, HENRY H. 1915 The rat. Data and reference tables. Memoirs of the Wistar Institute of Anatomy and Biology, no. 6. Philadelphia.

DURIG, A. 1901 Wassergehalt und Organfunktion. Erste Mitth. Arch. f. die gesamte Physiol., Bd. 85, S. 401–504.

FALCK, P., UND SCHEFFER, T. 1854 Untersuchungen über den Wassergehalt der Organe durstender und nicht durstender Hunde. Arch. f. physiol. Heilkunde, Bd. 13, S. 508–522. (Cited by Tobler, '10.)

HAMMAR, J. A. 1906 Ueber Gewicht, Involution und Persistenz der Thymus im Postfetalleben des Menschen. Arch. f. Anat. u. Phys., Anat. Abt.

HATAI, S. 1914 On the weight of the thymus gland of the albino rat (Mus norvegicus albinus) according to age. Am. Jour. Anat., vol. 16, pp. 251–257.

1918 On the weight of the epididymis, pancreas, stomach and of the submaxillary glands of the albino rat (Mus norvegicus albinus) according to body-weight. Am. Jour. Anat., vol. 24, no. 1.

JACKSON, C. M. 1913 Postnatal growth and variability of the body and of the various organs in the albino rat. Am. Jour. Anat., vol. 15, pp. 1–68.

1915 Effects of acute and chronic inanition upon the relative weights of the various organs and systems of adult albino rats. Am. Jour. Anat., vol. 18, pp. 75–116.

KUMAGAWA, M., UND MIURA, R. 1898 Zur Frage der Zuckerbildung aus Fett im Thierkörper. Arch. f. Physiol., S. 431–450.

LANDAUER, A. 1895 Ueber den Einfluss des Wassers auf den Organismus. Ung. Arch. f. Med., Bd. 3, S. 136–188. (Cited by Rosenstern, '11.)

LASAREW, N. 1895 Zur Lehre von der Veränderung des Gewichts und der zelligen Elemente einiger Organe und Gewebe in verschiedenen Perioden des vollständigen Hungerns. Dissertation, Warschau. (Cited by Mühlmann, '99.)

LUKJANOW, S. M. 1889 Ueber den Gehalt der Organe und Gewebe an Wasser und festen Bestandtheilen bei hungernden und durstenden Tauben im Vergleich mit dem bezüglichen Gehalt bei normalen Tauben. Zeitschr. f. physiol. Chemie, Bd. 13, S. 339–351.

McCARRISON, R. 1919 The pathogenesis of deficiency disease. Parts I to IX. Indian Jour. Med. Research, vol. 6, nos. 3, 4; vol. 7, nos. 1, 2. (Abstr. in Brit. Med. Jour., (1919) Feb. 15, p. 177; July 12, p. 36; Aug. 16, p. 200.)

MÜHLMANN, M. 1899 Russische Literatur über die Pathologie des Hungerns. Centralbl. f. allgem. Path. und pathol. Anat., Bd. 10, S. 160–220.

NOTHWANG, J. (F.) 1891 Die Folgen der Wasserentziehung. Arch. f. Hyg., Bd. 16, S. 122; Bd. 18, S. 83. Also, Dissertation, Marburg. (Cited by Tobler, '10.)

PERNICE, B., UND SCAGLIOSI, G. 1895 Ueber die Wirkung der Wasserentziehung auf Thiere. (Virchow's) Arch. f. path. Anat., Bd. 139, S. 155–184.

ROSENSTERN, J. 1911 Ueber Inanition im Säuglingsalter. Ergebn d. inneren Med. u. Kinderheilk., Bd. 7, S. 332–404.

SCHEFFER, TH. 1852 De animalium, aqua iis adempta, nutritione. Diss. Marburg. (Cited by Tobler, '10.)

SCHUCHARDT, B. 1847 Quaedam de effectu, quem privatio singularum partium, etc. Dissertation, Marburg. (Cited by Tobler, '10.)

SEDLMAIR, A. C. 1899 Ueber die Abnahme der Organe, insbesondere der Knochen, beim Hunger. Zeitschr. f. Biol., Bd. 37 (N. F. Bd. 19), S. 25–58.

SKORITSCHENKO 1883 Untersuchungen über einige Factoren des Hungerns. Protokolle der Conferenzsitzungen der Kais. Mil. Med. Akad., S. 175–233. (Cited by Mühlmann, '99.)

TIEDEMANN, F. 1836 Physiologie des Menschen, Bd. 3.

TOBLER, L. 1910 Zur Kenntniss des Chemismus akuter Gewichtsstürze. Beziehungen zwischen Wasser und Salzen im Organismus. Arch. f. exper. Pathol., Bd. 62, S. 431–468.

VOIT, CARL 1866 Ueber die Verschiedenheiten der Eiweisszersetzung beim Hungern. Zeitschr. f. Biol., Bd. 2, S. 308–365.

ZABAVER, DORA 1904 La mort par la soif. Th. Med. Lyon.

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STUDIES ON THE EFFECTS OF THIRST

II. EFFECTS OF THIRST UPON THE GROWTH OF THE BODY AND OF THE VARIOUS ORGANS IN YOUNG ALBINO RATS

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CONTENTS

Material and methods.......... 436
General observations.......... 441
Length of body and tail.......... 444
Integument.......... 445
Skeleton.......... 445
Musculature.......... 447
Viscera and 'remainder'.......... 447
Brain.......... 448
Spinal cord.......... 449
Sciatic nerves.......... 449
Eyeballs.......... 449
Heart and aorta.......... 450
Spleen.......... 451
Lungs.......... 452
Salivary glands.......... 452
Liver.......... 452
Pancreas.......... 453
Stomach and intestines.......... 453
Kidneys.......... 454
Testes.......... 454
Epididymides.......... 455
Ovaries.......... 455
Uterus.......... 455
Thyroid gland.......... 456
Thymus.......... 456
Suprarenal glands.......... 456
Hypophysis.......... 457
Discussion.......... 457
Summary.......... 459
Literature cited.......... 460
Tables.......... 439; 442

It has been shown by various investigators that if young animals are underfed so as to prevent an increase in body weight, changes nevertheless occur in various parts of the body. Some organs remain nearly constant in weight, others lose, and still others show a remarkably persistent growth in spite of the underfeeding. Since for growth water is no less essential than food (as demonstrated for the human infant by Meyer, '13), it is of interest to determine whether similar changes occur in the organs of young animals in which growth is prevented by a restriction of the water in the diet. The present investigation was undertaken for this purpose.

The work was done in the Institute of Anatomy of the University of Minnesota. This opportunity is taken to express my indebtedness to Dr. C. M. Jackson, Director of the Department, for valuable aid and direction.

MATERIAL AND METHODS

The albino rat (Mus norvegicus albinus) was chosen as the most convenient form for experiment. Postnatal growth norms for the body and various organs are available for comparison (Donaldson, '15). The changes in the weights of the organs have also been studied in young rats during underfeeding (Jackson, '15 a; Stewart, '18, '19) and in adult rats on a dry diet (Kudo, '21).

The material used in the present experiment included fifty-six individuals in all. The forty-one survivors (from eight litters) are listed in table 1. In the first column the letter (K) indicates the series, the number preceding the decimal point designates the the litter, and the number following is for the individual rat. The letter "m" signifies male; "f" female. Litters K5, K7, K8, K9, K10, K11, K12, K13, and K14 include, respectively, 4, 1, 5, 2, 8, 3, 5, 2, and 11 individuals. These include 17 males and 24 females, a total of 41. In addition 15 rats died during the test. They are excluded from the tables because the coagulated blood due to postmortem congestion might affect the weights of the organs.

In most cases the experiment began when the rats were about four weeks of age. Some of the experiments began at the age of three weeks (time of weaning), but most of these rats died.

Of the 41 rats listed, 11 were used for controls and the other 30 for the tests. The test rats were held at nearly constant body weight for varying periods as follows: for about 1 week (3 females); 2 weeks (2 males, 1 female); 3 weeks (4 males, 2 females); 4 weeks (2 males); 5 weeks (2 males, 2 females); 6 weeks (1 male, 1 female); 7 weeks (1 male, 3 females); 8 weeks (1 female); 9 weeks (1 male, 2 females); 11 weeks (1 female); and 13 weeks (1 female). Of the 30 test rats listed in table 1, one (K9.2 m.) of the 9-weeks' group was omitted, on account of its large body weight, from the corresponding group in table 2.

Eight normal controls (3 males, 5 females) were killed at the beginning of the experiment. The additional normal controls (K5.2, K 5.3, K 8.5) were killed at the end of the time periods indicated. These, and also two of the other controls (K7.1 and K9.1) are not used in table 2, because their body weights are too great for direct comparison with the test rats. A large number of observations upon normal rats previously published by Donaldson, Hatai, Jackson, Lowrey, and others are also available for comparison.

During the experiment the rats were kept each in a separate cage with wire-net bottom, allowing the feces and urine to drop through, which might otherwise be eaten. Both feces and food were carefully weighed. The rats were individually weighed daily before feeding. Those under experiment were allowed dry food ad libitum, together with whole milk carefully regulated in amount so as to hold them nearly constant at the initial body weight. Of course, slight fluctuations in the gross body weight were unavoidable, but they rarely exceeded 2 grams above or below the initial weight, as shown in table 1. The final gross body weight is in all cases nearly the same as the initial weight.

The temperature of the animal room was fairly constant at about 75° Fahrenheit (extreme range 65° to 80°).

Various methods of feeding were used. The eight initial controls were killed shortly after weaning (which occurs at the age of about three weeks), being subsequently fed on Graham bread and whole milk. Two control rats (K5.2, K8.5) were fed with dry 'dog-biscuit' (composition given by Kudo, '21) and water ad libitum, together with 5 to 15 grams of whole milk daily. One control rat (K5.2) was fed with maize (Indian corn) with milk and water. These grew normally up to the ages indicated in table 1.

The test rats (held at nearly constant body weight) were variously fed as follows:

1. Twenty rats (including all the test rats except those specified below) were fed with dry 'dog-biscuit' ad libitum. They consumed an average of about 3.7 grams daily. The amount of milk fed daily decreased from about 3.5 to 4 grams at first to less than 2 grams after three or four weeks. In experiments extending more than a month, however, it was necessary to increase the amount of milk again to 2.5 or 3 grams daily. Feces averaged about 0.8 gram daily throughout the experiment.

2. Five rats (K14.5, K14.9, K10.9 K13.3 and K10.8) were fed with crushed maize. Each rat consumed daily about 3.5 grams. The amount of milk fed decreased from about 3.5 to 4 grams daily at first to about 1 gram after three or four weeks. The feces averaged 0.7 gram daily.

3. Two rats (K14.4 and K14.3) were fed with a mixture of crushed maize and 'dog-biscuit.' They ate about 3.6 grams daily of that mixture and were fed about the same amount of milk as in (2). The feces averaged about 0.8 gram daily.

4. Two rats (K11.3 and K12.1) were fed with milk powder ('Klim' brand). They consumed a daily average of about 3.4 grams of the dry powder. In addition fresh whole milk was fed, decreasing from about 5 grams at first to less than 2 grams after a month.

5. One rat (K14.2) was fed with dried polished rice. It daily ate 3.8 grams of rice throughout the experiment and passed an average of 0.7 gram of feces. At first, milk was added to the diet as follows. In the first two weeks of the test the rat was fed milk in amounts decreasing from 1.8 to 0.7 gram daily; then for about three weeks with 0.5 to 0.1 gram of milk daily. In the final period of four weeks the rat was fed with dry rice only. In that period the body weight was reduced from 33.5 grams to 27.1 grams. This rat was very active and showed no evident symptoms of vitamine deficiency.

TABLE 1

Individual data on rats used

RAT NUMBER AND SEX	FINAL GROSS BODY WEIGHT (AND RANGE)	FINAL NET BODY WEIGHT	BODY LENGTH	AGE OF RAT, DAYS	
				Initial	Final
A. Normal controls					
	grams	*grams*	*cm.*		
K12.3 f	22.7	20.5	8.8	25	
K12.2 f	24.0	22.6	9.4	25	
K11.0 f	25.4	23.4	9.6	31	
K 8.1 f	29.3	23.7	9.9	32	
K 5.1 m	27.8	27.2	11.1	26	
K14.0 m	28.1	26.0	9.8	30	
K 7.1 f	36.4	34.4	10.5	35	
K 9.1 m	43.5	41.2	12.0	40	
K 5.3 m	115.7	108.2	16.2	24	56
K 5.2 f	121.5	114.5	16.8	28	77
K 8.5 f	146.5	142.5	18.4	28	112
B. Test rats (held nearly at maintenance)					
K11.4 f	19.9 (19.9–26.2)	18.5	8.8	27	33
K13.2 f	21.9 (21.9–25.0)	18.9	9.0	27	33
K11.3 f	21.9 (21.9–26.8)	20.5	9.7	28	34
K14.1 f	25.4 (25.0–28.8)	22.9	9.3	30	41
K 8.2 m	29.1 (27.7–29.9)	24.5	9.5	32	47
K 8.3 m	29.6 (25.8–31.0)	26.3	9.7	32	50
K14.4 m	23.0 (23.0–30.7)	21.1	9.3	28	49
K14.7 m	23.7 (23.7–32.1)	21.6	8.7	29	49
K14.8 m	25.6 (23.2–30.7)	22.6	10.1	29	51
K14.10 f	26.8 (24.7–31.6)	23.3	10.3	32	53
K14.5 m	26.6 (25.7–30.0)	23.4	9.9	28	50
K14.9 f	26.1 (25.5–31.0)	23.7	10.4	30	50
K14.3 m	24.7 (24.2–33.9)	22.7	9.5	28	54
K10.9 m	25.6 (23.6–30.0)	23.0	10.4	29	58
K14.6 f	28.3 (24.8–31.5)	25.6	9.4	28	62
K10.6 m	23.1 (23.1–28.4)	20.1	9.1	28	65
K10.3 m	26.6 (26.6–31.8)	23.9	10.5	28	65
K13.3 f	24.9 (22.6–29.3)	22.6	8.9	32	71
K12.1 f	25.3 (23.8–30.5)	23.6	9.0	25	67
K 5.4 m	36.2 (23.1–36.8)	33.3	11.3	33	79
K10.4 m	25.4 (24.0–28.7)	23.1	10.1	28	74
K12.5 f	28.3 (26.0–29.2)	24.1	10.3	28	76
K10.1 f	28.7 (28.1–31.9)	26.8	10.7	28	77
K10.2 f	30.1 (26.6–31.8)	25.7	10.5	28	78
K10.8 f	24.6 (23.6–29.6)	22.6	8.9	28	87
K 8.4 f	30.3 (25.2–32.1)	26.8	9.8	32	95
K14.2 f	26.9 (26.9–36.7)	25.0	10.5	28	95
K 9.2 m	43.5 (38.2–49.0)	39.1	11.9	40	104
K10.5 f	26.0 (23.7–26.8)	21.9	9.7	28	104
K12.4 f	28.1 (26.3–32.0)	25.8	10.4	28	117

While no exact chemical determinations were made, it is evident that the amounts of food consumed by the rats in these thirst experiments are more than sufficient for maintenanance when water is allowed at libitum. Under these circumstances, Jackson ('15) found that rats of about 24 grams in body weight require for maintenance only about 5 grams daily of Graham bread soaked in whole milk; decreasing to about 3 grams later. Since a greater amount of food was consumed by my rats on the thirst experiments, it is evident that the prevention of growth is due to the lack of water rather than to inanition from inadequate food-intake.

In the inanition experiments with water (Jackson, '15 a) the amount of food required for maintenance of body weight in young rats was found to decrease as the experiment proceeds. Similarly in the present tests (as above shown) a decreasing amount of liquid (milk) is required for maintenance with dry food ad libitum, although the amount of dry food taken remains fairly constant.

The difference in the amount of milk required for maintenance of body weight with the different kinds of food probably depends (at least in part) upon the amount of water contained in the food. In all cases, however, there is a decrease in the milk required as the experiment proceeds. Jackson ('15 a) thought that in young rats held at maintenance by underfeeding the amount of living protoplasm is greatly decreased, thereby decreasing the basal rate of metabolism, with a corresponding decrease in the necessary food-intake. Possibly a similar explanation may hold in the case of the present thirst experiments. The metabolism may be altered in some way so as to require less water for maintenance of constant body weight.

Both test rats and controls were killed by chloroform and dissected according to the technique described by Donaldson ('15), with a few modifications. The submaxillary gland and thyroid gland were removed first. The parts and organs upon removal were placed in a closed jar upon glass plates resting on moist filter-paper. After weighing, the organs were dried to constant weight in an oven at about 95°C. in order to determine their water content (not included in this paper).

Percentage losses in the various organs were calculated as follows. The average weight (table 2) for each organ or part in the test rats was compared with the corresponding average for the normal controls of similar body weight. The data in the column 'Difference' express the apparent percentage changes (+ or −) as the result of the experiment. In table 2 the average gross body weight and net body weight (gross body weight minus intestinal contents) are seen to differ but slightly (usually less than 5 per cent) in the various test groups, as compared with the normal controls. These differences have been ignored in calculating the percentage changes for the various parts.

In view of the comparatively small number of observations and the known variability, especially of some of the organs (Jackson, '13), the conclusions reached in the present paper are by no means to be considered as final. It is believed, however, that they are sufficient to give an approximate idea of some of the more obvious and important changes, so as to make possible a comparison of the effects of a relatively dry diet (water deficiency) with other forms of inanition.

GENERAL OBSERVATIONS

In general the test rats remained active and apparently healthy, although many died during the course of the experiment, as above stated. The skin becomes somewhat roughened, but the hair is not easily detached (as occurs in adults during thirst). Dryness and desquamation were observed on the plantar surfaces. The claws become much elongated, especially in the later test periods. The fecal material is usually hard, never diarrheal in character. The urine is scanty. Haemorrhage from the conjunctiva or nose was not observed, although it sometimes occurred in the stomach or intestines. In the rats dying during the experiments (not included in the tables) hemorrhage and ulceration of the stomach were often observed. Dryness of the external genital organs, especially in females, was observed, and eczematous conditions often occurred in the longer experiments. Paralysis of the legs or other parts was never found in the young rats (as noted occasionally in adults by Kudo, '21). In some young rats the

TABLE 2

Average data for controls and test rats, with percentage of change in the various test groups, as compared with normal controls. Weights are given in grams, lengths in centimeters

	NORMAL CONTROLS (2M; 4F) AGE 25 TO 30 DAYS. AVERAGE	TEST RATS ON DRY DIET HELD AT CONSTANT BODY WEIGHT FOR PERIODS INDICATED				
		1 to 2 weeks (2m; 4f) Average and percentage difference	3 to 4 weeks (6m; 2f, Average and percentage difference	5 to 6 weeks (3m; 3f) Average and percentage difference	7 to 8 weeks (1m: 4f) Average and percentage difference	9 to 13 weeks (0m; 4f) Average and percentage difference
Gross body weight....	26.2	24.6 (−6.1)	25.3 (−3.4)	27.4 (+4.6)	27.4 (+4.6)	27.8 (+4.6)
Net body weight......	23.7	22.4 (−5.5)	22.7 (−4.2)	24.9 (+5.1)	24.4 (+3.0)	24.9 (+5.1)
Body length..........	9.8	9.3 (−5.1)	9.8 (0)	9.9 (+1.0)	101. (+3.1)	10.1 (+3.1)
Tail length...........	7.0	7.4 (+5.7)	8.7 (+24.3)	8.4 (+20.0)	8.8 (+25.7)	9.0 (+28.6)
Integument...........	4.35	3.74 (−14.0)	3.91 (−10.2)	3.48 (−10.0)	3.97 (−8.7)	3.98 (−7.5)
Musculature..........	7.32	6.81 (−7.0)	6.98 (−4.7)	7.38 (+0.8)	6.82 (−6.8)	6.97 (−4.8)
Lig. skeleton..........	3.73	4.26 (+14.2)	4.59 (+23.1)	5.09 (+36.5)	5.22 (+40.0)	5.06 (+35.7)
Cart. skeleton.........	2.79	3.80 (+36.2)	3.42 (+22.6)	4.17 (+49.5)	4.29 (+53.8)	4.42 (+58.4)
Humeri and femurs...	0.3355	0.3856 (+14.9)	0.4026 (+20.0)	0.4540 (+35.3)	0.4152 (+23.7)	0.4439 (+32.3)
Visceral group........	5.1912	5.3501 (+3.1)	5.4883 (+5.7)	5.6224 (+8.3)	6.1769 (+19.0)	6.2578 (+20.6)
Remainder............	1.10	0.51 (−37.3)	0.58 (−47.3)	0.64 (−41.9)	0.59 (−46.4)	0.54 (−50.9)
Brain.................	1.2424	1.1894 (−4.3)	1.3088 (+5.4)	1.2583 (+1.3)	1.2636 (+1.7)	1.3493 (+8.6)
Spinal cord...........	0.1565	0.1891 (+20.8)	0.2107 (+34.6)	0.2165 (+38.2)	0.2389 (+52.5)	0.2398 (+53.1)
Nn. ischiadici.........	0.0087	0.0090 (+3.5)	0.0119 (+36.8)	0.0111 (+27.6)	0.0123 (+41.4)	0.0129 (+48.3)
Eyeballs..............	0.1054	0.1152 (+9.3)	0.1456 (+3.83)	0.1448 (+37.5)	0.1719 (+63.3)	0.1797 (+70.8)
Heart.................	0.1696	0.1557 (−8.2)	0.1547 (−8.8)	0.1695 (+0.06)	0.1963 (+15.8)	0.1873 (+10.4)
Spleen................	0.0838	0.0432 (−48.4)	0.0474 (−43.5)	0.0436 (−48.0)	0.0762 (−9.1)	0.1136 (+36.6) 0.0523 (−37.6)
Lungs.................	0.2369	0.2145 (−9.5)	0.2310 (−2.5)	0.2452 (+3.5)	0.2363 (−0.25)	0.2294 (−2.8)
Parotid glands........	0.0284	0.0149 (−47.6)	0.0152 (−46.5)	0.0115 (−59.6)	0.0160 (−43.7)	0.0155 (−45.4)
Submaxillary glands..	0.1010	0.0759 (−24.9)	0.0573 (−43.3)	0.0415 (−59.0)	0.0512 (−49.3)	0.0598 (−40.8)
Liver.................	1.1636	1.3244 (+13.8)	1.2313 (+5.8)	1.3045 (+12.1)	1.2363 (+6.3)	1.5522 (+33.5)
Pancreas..............	0.1389	0.1610 (+15.9)	0.1795 (+29.2)	0.1722 (+24.0)	0.1846 (+32.9)	0.2032 (+46.3)

Stomach-intestines (with contents)	3.60	3.65 (+1.4)	3.94 (+9.4)	4.00 (+11.1)	4.65 (+29.2)	4.70 (+30.6)
Stomach-intestines (empty)	1.30	1.38 (+6.2)	1.36 (+4.6)	1.44 (+10.8)	1.68 (+29.3)	1.75 (+34.6)
Kidneys	0.2988	0.4034 (+35.0)	0.4451 (+48.4)	0.4797 (+60.5)	0.4940 (+65.3)	0.4435 (+48.4)
Testes	0.1427	0.0962 (−32.5)	0.0748 (−47.5)	0.1005 (−29.5)	0.0450 (−68.3)	
Epididymides	0.0190	0.0144 (−24.2)	0.0147 (−22.6)	0.0128 (−32.6)	0.0132 (−30.5)	
Ovaries	0.0114	0.0077 (−32.5)	0.0061 (−46.5)	0.0041 (−64.0)	0.0043 (−62.3)	0.0038 (−66.7)
Uterus	0.0161	0.0138 (−14.3)	0.0174 (+8.1)	0.0136 (−15.5)	0.0204 (+26.7)	0.0217 (+34.8)
Thyroid	0.0038	0.0033 (−13.1)	0.0035 (−7.9)	0.0032 (−15.8)	0.0028 (−26.3)	0.0039 (+2.6)
Thymus	0.0771	0.0240 (−68.9)	0.0094 (−87.8)	0.0134 (−82.6)	0.0109 (−85.9)	0.0067 (−91.3)
Suprarenals (m)	0.0077	0.0124 (+61.0)			0.0132 (+71.4)	
Suprarenals (f)		0.0106 (+37.7)			0.0128 (+66.2)	
Hypophysis (m)	0.0016	0.0017 (+6.3)			0.0023 (+43.8)	
Hypophysis (f)		0.0015 (−6.3)			0.0022 (+37.5)	

penis was extruded, possibly from attempts to get the urine. It is to be noted that the specific symptoms generally found associated with various vitamine deficiencies are either slight or entirely absent in survivors of these thirst experiments.

The general condition observed at autopsy are as follows: There is extreme general emaciation, especially in the longer periods. The skin and muscles appear somewhat dry and difficult to separate. The blood is thick. The fat has usually almost disappeared from the subcutaneous and muscular tissues; but in some cases it remains in relatively large amount. The orbital and interscapular fat persists in small amount even in the longer experiments. There is no appreciable change in amount of serous fluid in the pericardial, pleural, and peritoneal cavities. The viscera generally appear normal. The liver is often congested and occasionally yellowish in color (fatty change?). The kidneys are often congested, and their surfaces appear rough in a few cases. Marked congestion of the brain, kidneys, suprarenals, spleen, and lungs was sometimes found. In general, however, the effects of thirst on young rats, as shown by observations and autopsy, appear slighter than in adult rats.

LENGTH OF BODY AND TAIL

The body length is measured from the tip of the nose to the anus and the tail length from the anus to the tip of the tail. The measurements were taken immediately after death, the body and tail being extended by very slight tension. Measurements during life are not very accurate, although they might be obtained by the use of anesthetics. Some measurements were made on the living animals, however, which show changes in the lengths of body and tail similar to the changes indicated by the measurements at autopsy.

In the groups of rats held at constant body weight for the five periods (table 2) the percentage changes in average body length are insignificant, usually corresponding to the slight differences in body weight between test rats and controls. It is evident that the body length remains nearly constant. The tail length, however, shows a marked and progressive increase, indicating for the five periods gains of 5.7, 24.3, 20.0, 25.7, and 28.6 per cent, respectively (table 2).

Thus the rats held at constant body weight by thirst become relatively long-tailed, as found likewise by Jackson ('15 a) in young rats held at maintenance by underfeeding. Some data indicating an opposite result were reported by Hatai ('08).

In adult rats during thirst the body length in the acute series shows an average loss of 11.4 per cent and in the chronic-thirst series a loss of 14.7 per cent. The tail, however, has nearly the same average length in controls and test rats (Kudo, '21).

INTEGUMENT

The general changes in the integument were mentioned above under 'General Observations.' In the young rats held at constant body weight in five test series (table 2) there is a slight apparent loss varying from 7.5 to 14 per cent in weight of the integument (which includes the skin and appendages, hair and claws). It would appear that this slight loss occurs early, and is not progressive during the course of the experiment.

In adult rats during thirst the loss of the integument is very nearly proportional to that of the whole body (Kudo, '21).

In inanition (with water) a much greater loss of 36 per cent or more was found in the weight of the integument of young rats by Jackson ('15 a).

SKELETON

The bones, together with the cartilages, periosteum, and ligaments, constitute the 'ligamentous skeleton.' The bones and cartilages, after removal of the periosteum and ligaments by immersion for about one hour in 1 per cent aqueous 'Gold Dust' (a commercial soap powder) solution at 90°C., constitute the 'cartilaginous skeleton.' Donaldson and Conrow ('19) have shown that while such a maceration in hot 'Gold Dust' solution causes only a slight loss (less than 5 per cent) in the skeleton of adult rats, in young rats the loss in skeletal weight is considerably greater, amounting to about 15 per cent in the new born. The humerus and femur (of both sides) were therefore cleaned separately without maceration, and their weights are recorded separately in table 2, though also included in the weights of the whole skeleton.

As shown by table 2, while the body weight is held constant during the thirst experiments, the ligamentous skeleton continues to increase in weight to a marked degree. The increase is progressive from 14.2 per cent at one to two weeks up to 40 per cent at seven to eight weeks (slightly less at nine to thirteen weeks). For the cartilaginous skeleton the apparent increase in weight is still greater, ranging from 22.6 to 58.4 per cent. It is possible that these large percentages (especially that of 36.2 per cent at one to two weeks) may be erroneous, due to abnormalities or to errors in technique.

The humerus and femur (weighed separately in the moist cartilaginous state, after removal of periosteum and ligaments without immersion in the hot soap solution), as shown in table 2, show percentage increases which are very close to those of the ligamentous skeleton, and these probably form a more accurate index of the actual changes in the weight of the cartilaginous skeleton.

In an underfeeding experiment, Jackson ('15 a) found that the increase in young rats held at constant body weight from three to ten weeks of age forms 28 per cent in the weight of the ligamentous skeleton, and 21.5 per cent in the weight of the cartilaginous skeleton which is somewhat lower than that obtained in the present thirst experiments. This may be because less water is required for the growth of bone, so that its growth is less retarded on a relatively dry diet.

In the inanition experiment on young rats, Jackson ('15 a) noted that the skeletal growth tends to proceed along the lines of normal development, as indicated by decrease in the water content, by formation and union of various epiphyses, etc. Very similar phenomena were noted in the skeleton during the present thirst experiments (epiphyses of vertebrae and humerus, appearance of third molars, etc.).

Data cited by Jackson from other investigators (Waters, Aron, Variot) indicate that a persistent growth of the skeleton during inanition likewise occurs in the young of other species (calves, puppies, human infants). Jackson and Stewart have shown that the growth of the skeleton in underfed rats appears less intensive in very young (newborn) rats and in older rats (approaching maturity).

MUSCULATURE

As shown in table 2, the various groups of tests rat show apparent slight decreases (4.7 to 7 per cent) in weight, excepting the third group, which is nearly constant. These differences are insignificant, especially when the slight differences in body weight between controls and test rats are taken into account, but there is perhaps a slight tendency to decrease in the later periods.

In young rats held at constant body weight by inanition (simple underfeeding) the musculature, as in thirst, also remains nearly constant, but with a very slight tendency to increase in weight (Jackson, '15 a).

During thirst in adult rats the musculature loses approximately in proportion to the entire body (Kudo, '21).

VISCERA AND 'REMAINDER'

The visceral group includes the brain, spinal cord, hypophysis, and eyeballs, as well as thoracic and abdominal viscera. In the animals held at constant body weight (table 2) the visceral group shows a progressive increase in weight of 3.1 to 20.6 per cent in the five test series.

The weight of the visceral group depends essentially upon that of the larger organs. As will be seen later, however the individual viscera differ greatly in their changes in weight during the thirst experiments.

In the maintenance of the body weight by simple inanition, Jackson ('15 a), in young albino rats, and Aron ('11), in young dogs, found that the visceral group undergoes but little change in weight.

The 'remainder' is that part of the body which remains after removing the skin, skeleton, musculature, and visceral group. It includes the adipose and interstitial connective tissue, mesenterium, larger peripheral nerves, and blood-vessels, etc. The escaped fluids and the loss by evaporation are not included. As shown in table 2, the 'remainder' in the various tests undergoes a loss in weight increasing from 37.3 per cent in the one to two weeks' test to 50.9 per cent in nine to thirteen weeks. This loss is probably chiefly due to that of the fat, which largely disappears, as mentioned under 'General Observations.'

BRAIN

The brain weight of the control rats (table 2) corresponds closely to the data of Donaldson ('15) and Jackson ('15a). In the rats at the various test periods the average brain weight shows slight apparent changes, varying from −4.3 per cent to +8.6 per cent. It will be noted, however, that (with one exception) these apparent changes are in the same direction as the corresponding slight differences between test rats and controls in average body weight. The apparent differences in brain weight are therefore insignificant, considering the small number of observations, and it seems probable that the brain undergoes no appreciable change in weight during these thirst experiments.

Hatai ('04) found a slight apparent loss (average about 4.7 per cent) in the weight of the brain in young albino rats fed with starch, beef fat, and water, the body weight being reduced about 30 per cent (average). In a later experiment, however, Hatai ('08) found that the growth in brain weight was retarded in the same proportion as the whole body weight. In albino rats with retarded growth on a lipoid-free ration, the brain was apparently about 2 per cent subnormal in weight (Hatai, '15).

In underfed young rats (with water), Donaldson ('11) found an apparent slight increase (3.6 per cent) in the brain weight, while Jackson ('15 a) found no significant change. It is evident that the age at which the inanition occurs is important, as Stewart ('18, '19) found a marked increase (125 per cent) in the brain of newborn rats held at constant body weight by underfeeding for sixteen days. Variot and Lassabliere ('09) observed a tendency to persistent growth in brain weight in human infants whose body weight was retarded by malnutrition. The brain weight of the adult rats subjected to thirst showed no significant change in weight (Kudo, '21). The constancy of the brain weight in adults under various forms of inanition has been repeatedly observed by numerous investigators. McCarrison ('19), however, finds an apparent increase of one-seventh in the brain weight of monkeys on various diets deficient in vitamines.

SPINAL CORD

The spinal cord shows a marked and progressive increase (20.8 to 53.1 per cent) in weight in the various test periods (table 2).

Jackson ('15 a) found an increase of 36 per cent in the spinal cord of rats held at constant body weight by underfeeding from three to ten weeks of age, and a smaller increase was obtained by Donaldson ('11). In newborn rats, held at maintenance by underfeeding from sixteen days, Stewart ('19) found an increase of 83 per cent in the weight of the spinal cord. In the thirst experiments on adult rats, the spinal cord shows but little change in weight (Kudo, '21).

SCIATIC NERVES

The sciatic nerves (nn. ischiadici) in the test rats showed an increase in weight which is similar to that of the spinal cord, excepting the first period (table 2). This indicates that the continued growth of the spinal cord is correlated with that of the peripheral nerves, as might be expected. In the thirst experiments on adult albino rats, however, the sciatic nerves lost in weight, while the spinal cord did not. No further data on the changes in weight of peripheral nerves during inanition have been found in the literature.

EYEBALLS

The eyeballs likewise show a marked and progressive increase in average weight during the various test periods (table 2), varying from 9.3 to 70.8 per cent. The apparent increase of 70.8 per cent in weight of the eyeballs during the thirst experiments is greater than that observed in any other organ or system.

In the adult rats the eyeballs lose nearly 10 per cent during thirst (Kudo, '21). In young rats underfed (with water) from three to ten weeks of age, Jackson ('15 a) found an increase of nearly 50 per cent in the weight of the eyeballs. A still greater increase (146 per cent) was found by Stewart ('19) in similar experiments on newborn rats.

Jackson ('15 a) thought the striking growth capacity of the eyeballs during inanition might depend upon their large water absorption, as the eyeballs are known to have a very high water content. The present thirst experiments, however, indicate that the remarkably persistent growth of the eyeballs continues even when the water supply to the organism is greatly restricted.

Notwithstanding the great increase in the size of the eyeballs in the test rats, they do not protrude abnormally. More space is doubtless provided for them, partly by actual growth of the skeletal orbit and partly by atrophy of the orbital fat.

HEART AND AORTA

The heart (table 2) in the test rats shows an apparent slight decrease in weight in the earlier periods with a small increase in the later periods of thirst. It will be noted, however, that these changes do not greatly exceed the differences between test rats and controls in body weight, which are in the same direction. The apparent changes in heart weight are therefore of doubtful significance.

In rats underfed from three weeks of age, Jackson ('15 a) likewise found no significant change of weight, although in underfed newborn rats Stewart ('19) noted an increase of 26 per cent.

During thirst in adult rats the heart likewise maintains its relative weight, losing in absolute weight nearly in proportion to the entire body (Kudo, '21).

Aorta. The aorta was cut proximally at the heart and distally at the origin of the iliac branches. All branches of the aorta were clipped close to the vessel. All blood content was removed. The following observations are too few (especially on controls) to warrant conclusions, but would seem to indicate an increase in the weight of the aorta during the thirst experiments.

LENGTH OF TEST	NUMBER OF RATS	AVERAGE NET BODY WEIGHT	AVERAGE WEIGHT OF AORTA
		grams	*gram*
(Control)	1	26.0	0.0187
1–2 weeks	2	20.9	0.0159
3–4 weeks	7	22.6	0.0212
5–6 weeks	3	23.9	0.0246
7–8 weeks	4	24.8	0.0232
9–13 weeks	3	24.2	0.0234

SPLEEN

The spleen (table 2) shows a marked loss in average weight (36.6 to 48.4 per cent) in all the test groups but one, in which the loss appears much smaller (9.1 per cent). The very small apparent loss in this test group is due to an abnormally large spleen which weighed 0.2 gram, which brought up the average for the group. If this abnormal spleen were excluded, the loss in this group would appear as 46.5 per cent. Similarly in the last group, the inclusion of an abnormally large spleen gives an apparent average increase of 36.6 per cent; omitting this spleen, there is an average loss of 37.6 per cent. Although the spleen is normally one of the most variable organs in the body (Jackson, '13), requiring caution in drawing conclusions, it is evident that it usually undergoes a great loss in weight in young rats held at constant body weight by thirst.

In adult albino rats during thirst, both acute and chronic, the spleen similarly loses relatively much more in weight than does the body as a whole (Kudo, '21). Jackson ('15 a) found that in young rats held at maintenance by underfeeding beginning at the age of three weeks there is a marked tendency to decrease in weight of the spleen, while at later (and longer) periods the spleen appears to undergo no material change in weight. In the underfed newborn rats, Stewart ('19) found an increase of 33 per cent in the spleen.

LUNGS

The lung infections frequently found in older rats rarely occur before the age of ten weeks (Jackson, '15 a) and did not occur in in the rats shown in tables 1 and 2. The average weight of the lungs in the test groups shows slight changes, varying from −9.5 to +3.5 per cent. These changes are usually in the same direction as the differences in average body weight, however, and are too small to be significant. It is therefore evident that there is but slight if any change in the weight of the lungs during the present thirst experiments.

During thirst in adult rats the percentage loss in the weight of the lungs appears slightly greater than that of the whole body (Kudo, '21). In young rats held at constant body weight by underfeeding, Jackson ('15 a) found a slight decrease in the early periods, but not in the later. There is no appreciable increase in the lungs of the underfed newborn rats (Stewart, '19).

SALIVARY GLANDS

Parotid glands. The parotid glands (table 2) show a marked decrease in average weight, varying from 43.7 to 59.6 per cent in the various test groups. This loss apparently occurs early and remains fairly uniform throughout the various test periods. In adult albino rats during thirst, both in acute and chronic, the percentage loss in weight of the parotid glands is likewise much larger than that of the entire body (Kudo, '21).

Submaxillary glands. A striking decrease in weight similar to that of the parotid glands is apparent in the submaxillary glands (table 2) in all except the first test group, where the loss (24.9 per cent) is somewhat smaller. In adult albino rats during thirst, both acute and chronic, the submaxillary glands likewise decrease in weight relatively much more than does the body as a whole (Kudo, '21).

LIVER

The liver shows somewhat irregular increases in average weight (table 2), varying from 5.8 to 33.5 per cent in the different test periods. While the liver thus shows a definite tendency to increase, caution must be observed in drawing conclusions, on account of the great variability in the weight of the normal liver (Jackson, '13).

In the adult rats during thirst the liver loses weight in about the same proportion as the whole body (Kudo, '21). In young rats underfed from three weeks of age the liver is variable, showing a definite increase in weight in the earlier periods, but a decrease later (Jackson, '15 a). Stewart ('19) found a marked loss in the liver weight of underfed newborn rats.

PANCREAS

The pancreas (table 2) in the various test periods shows a progressive increase in average weight (15.9 to 46.2 per cent). It may be noted that the average weight of the pancreas in my controls (0.1389 gram) is considerably below the corresponding weight found by Hatai ('18) (0.206 gram); but, as Hatai remarks, it is difficult to dissect out the gland with uniform accuracy.

In adult rats a decrease in weight of the pancreas during thirst is relatively much greater than that of the whole body. Thus the loss in the weight of the pancreas resembles that of the salivary glands.

STOMACH AND INTESTINES

The stomach and intestines were separated from mesentery and pancreas. The digestive tube with contents (table 2) shows a progressive increase in average weight, varying from 1.4 to 30.6 per cent. The increase is not significant until after six weeks. The data for the empty stomach and intestines show a very similar progressive increase in average weight, varying from 4.6 to 34.6 per cent. Thus both the alimentary canal and the intestinal contents appear to increase in weight, especially in the thirst experiments extending beyond six weeks in length. The intestinal contents in the test rats are watery or mucous in character in the small intestine, becoming usually very hard in the fecal material of the large intestine.

In rats underfed from three weeks of age Jackson ('15 a) likewise found an increase in the weight of the intestinal canal (plus mesentery and pancreas), which continued up to the age of six weeks, but appeared to decrease later. In adult ablino rats during thirst there is a marked decrease (relatively slightly less than that of the entire body) in the weight of the stomach and intestines (Kudo, '21).

KIDNEYS

The kidneys (table 2) in the test groups show a marked apparent increase in average weight, progressing from 35 to 65.3 per cent in the first four groups, but decreasing to a gain of only 48.4 per cent in the longest test (nine to thirteen weeks). It is possible, however, that the large apparent increase may be due in part to an abnormally low kidney weight in my controls, which is somewhat below the normals of Jackson ('15 a) and Donaldson ('15). In young rats underfed beginning at three weeks of age Jackson ('15 a) found a slight increase in the weight of the kidney, but little or no change at later periods. Stewart ('19) found a great increase (90 per cent) in the kidney weight of underfed newborn rats.

In adult rats during acute and chronic thirst the kidneys lose in weight relatively slightly less than the body as a whole (Kudo, '20).

TESTES

The average net body weights of the males in the various groups of table 2 are as follows: controls (2), 26.6 grams; 1–2 weeks (2), 26.7 grams; 3–4 weeks (6), 22.4 grams; 5–6 weeks (3), 25.8 grams; 7–8 weeks (1), 23.1. It is thus evident that the average body weights of the various test groups differ somewhat from the controls, which partly accounts for the greater apparent losses in the groups at three to four weeks and seven to eight weeks. Making allowance for this difference in body weight, the tests would show an average decrease of something over 30 per cent.

On the other hand, Jackson ('15 a) found an apparent increase of 34 per cent in the weight of the testis in rats underfed beginning at three weeks of age, and Stewart ('19) obtained an enormous increase (average 374 per cent) in the testes of newborn rats held at maintenance by underfeeding for about sixteen days.

In adult rats the testes during acute thirst lose about 15 per cent in their weight and during chronic thirst they lose 52.7 per cent, while the loss of the whole body is respectively 36.1 per cent and 52.4 per cent (Kudo, '21). Hatai ('15) found that the testes of young albino rats show an actual loss in weight (23 per cent) as a result of six months on the lipoid free-diet.

EPIDIDYMIDES

The apparent losses in the average weight of the epididymis (table 2) are, of course, subject to the same corrections as those of the testis, on account of differences in body weight between test rats and controls. The actual losses are therefore somewhat lower than those indicated in the table and below those of the testis.

In adult rats during thirst the epididymides lose weight roughly in proportion to the body weight (Kudo, '21).

OVARIES

The average body weight of the female rats in the control group (table 2) is slightly lower than that in all the test groups, excepting the first. But the maximum difference in body weight is only about 10 per cent, so the relatively large apparent losses in the average weight of the ovaries, increasing progressively from 32.5 to 66.7 per cent, would not be materially affected by the required corrections.

This loss in the weight of the ovaries during thirst is materially greater than that (27 per cent) found by Jackson ('15 a) in rats underfed beginning at three weeks of age. Stewart ('19) found practically no change in the weight of the ovaries in underfed newborn rats. Hatai ('15) found in young albino rats fed with lipoid-free diet a loss of 17.4 per cent in the weight of the ovaries.

UTERUS

The uterus (including tubes) is subject to considerable variation in weight, as appears in the various test groups in table 2. While the tendency during the earlier test periods is somewhat fluctuating and doubtful, there appears to be a definite increase in average weight (26.7 to 34.8 per cent) in the two longest tests. Its change in weight therefore appears quite different from that of the ovaries.

THYROID GLAND

The thyroid gland shows an apparent loss in average weight in all but the last test group (table 2). In most cases the difference is too small to be significant, however, especially when the individual variation in the weight of the thyroid gland and also the great difficulty in dissecting it out in a uniform manner are considered. Jackson ('15 a), however, found an apparent loss of about 24 per cent in the thyroid of rats underfed from three weeks of age.

In adult albino rats during thirst, both acute and chronic, the thyroid glands lose markedly in weight (Kudo, '21).

THYMUS

The loss of 68.9 to 91.3 per cent in the average weight of the thymus in the various test groups (table 2) is greater than that in any other organ. According to Hatai ('14), the thymus should reach its maximum absolute weight (0.29 gram) at about eighty-five days of age, after which it normally undergoes a slow age involution. As is well known, the thymus is especially liable to a rapid involution under various unfavorable circumstances ('accidental involution' of Hammar). This was found by Jackson ('15 a) in rats underfed at three weeks of age and later, and also by Stewart ('19) in newborn rats. In adult rats during thirst the involution of thymus is likewise very marked, with loss of about 90 per cent in weight (Kudo, '21).

SUPRARENAL GLANDS

In the suprarenal glands of the rat there is normally a sexual difference in weight, observable from the age of about six weeks (Jackson, '13, Hatai, '13). Before this age the sexes may safely be grouped together, as in my controls. In the test groups the sexes are separated, although on account of the small numbers and the irregularity of the data they are combined into only two age groups, one to four weeks and five to thirteen weeks. All four groups show a marked apparent increase in weight, which is about 60 per cent in all except the younger group of females (37.7 per cent). This difference is not on account of the appearance of the normal sex difference, however, for normally the suprarenals become larger in the female. As a matter of fact, the tendency to sexual difference in weight does not appear in these thirst experiments, (contrary to the observations of Jackon) ('15 a) in underfeeding).

In the rats underfed beginning at three weeks of age Jackson ('15 a) found an apparent increase of 12 to 39 per cent in the weight of the suprarenals. A much smaller increase (5 per cent) was found by Stewart (19) in underfed newborn rats.

In adult rats during thirst there is a relatively small loss in weight of the suprarenal glands (Kudo, '21).

HYPOPHYSIS

The hypophysis in rats above 50 grams in body weight must be considered separately in the sexes, since it then normally becomes relatively heavier in the female. This does not affect my controls (grouped together in table 2), and it is evident from table 2 that there likewise appears no sexual differentiation in weight in the test rats during the thirst experiments (in agreement with the inanition experiments of Jackson, '15 a). There is evidently no significant change in the average weight of the hypophysis in the one to four weeks' group, but a marked increase (37.5 to 43.8 per cent) in the five to thirteen weeks' group.

Jackson ('15 a) found a smaller increase (18 to 19 per cent) in the rats underfed from three weeks of age, while Stewart ('19) found a slightly larger increase in the underfed newborn rats.

In adult rats during thirst the hypophysis changes but little in absolute weight (Kudo, '21).

DISCUSSION

The changes in the average weights of the various organs and parts in rats held at constant body weight for the various periods are summarized in table 2. While no great emphasis can be laid upon the exact accuracy of the figures shown in table 2, it is evident that, with respect to the changes in weight during the thirst experiments, the organs may be divided into three groups. In the first group, which includes hypophysis, eyeballs, kidneys, suprarenals, spinal cord, skeleton, sciatic nerves, pancreas, alimentary canal, liver, humerus and femur, visceral group and uterus, there is a well-marked increase in weight during the maintenance of constant body weight by thirst in young rats. As shown in table 2, the rate of increase in the weight of the organs, in general, is progressively greater in the longer periods.

In the second group, which includes heart, brain, musculature, and lungs, the organs remain nearly constant in weight.

In the third group, including the thymus, ovaries, parotid and submaxillary glands, 'remainder,' spleen, testes, epididymides, thyroid, and integument, there is a marked loss in weight. This loss appears in most of the organs already in the earlier test periods and in some cases (thymus, thyroid) appears more or less progressive in character.

If we compare the changes in weight, as a measure of their relative resistance to thirst, in young growing rats with those observed in adult rats during acute and chronic thirst (Kudo, '21), it is found that in general there is in many cases a considerable degree of correspondence. The hypophysis, eyeballs, skeleton, and spinal cord increase in weight in the young rats and also show marked resistance (slight loss in weight) in adults during acute and chronic thirst. The brain in all cases remains nearly constant in weight.

The heart weight is nearly constant in the young rats and loses nearly in proportion to the body during adult thirst. The thymus, 'remainder,' salivary glands, spleen, testes, and epididymides lose weight markedly during thirst in both young and adult rats.

In many other cases, however, the changes in organ weight in the young differ materially in tendency from those in adult. Thus the pancreas and liver have a marked growth tendency in the young test rats, but lose heavily during adult thirst. Lesser degrees of difference are observed in many other organs.

Comparing my results in young rats on thirst tests with those of Jackson ('15 a) in young rats of similar age held at constant body weight by underfeeding (with water allowed), there is found a remarkable similarity between them. Thus, in both cases there is a marked growth in the brain, spinal cord, eyeballs, hypophysis, skeleton, suprarenals, and alimentary canal. In both series the brain, musculature, and heart remained nearly constant, and the thymus, ovaries, spleen, thyroid, and integument decreased greatly in weight. There are some differences between the results of the thirst and the inanition tests, however. The kidneys appear to gain markedly during thirst, but remain constant during inanition. The testes lose heavily in weight during thirst, but gain markedly during inanition. Other forms of partial inanition give results differing more or less from the foregoing, as shown by the experiments of Hatai, Osborne and Mendel, McCarrison, and others on diets defective in various respects, including vitamine deficiencies (cf. Jackson and Stewart, '19, and Kudo, '21).

It has also been shown by Jackson and Stewart that the changes in organ weight during inanition differ greatly according to the age of the animals. Thus, the changes during underfeeding in the newborn are very different from those in adolescent rats and these in turn differ from those in older animals. The age factor is doubtless equally important in the effects of thirst upon the weight of the various organs.

SUMMARY

The principal results of the present investigation may be briefly summarized as follows.

Albino rats about one month old may be held at constant body weight for several weeks by a restricted amount of liquid (milk) in a diet otherwise adequate for growth. The rats show a progressive tolerance of thirst, so that less liquid milk is daily required for maintenance as the experiment proceeds.

The tail becomes elongated while the body length remains constant.

There is in general a marked increase in the weight of the skeleton and a slight increase in the visceral group.

The musculature remains nearly constant in weight. There is a slight decrease in the integument and a marked loss in the 'reminder.' Of the individual viscera:

1. The hypophysis, eyeballs, kidneys, suprarenals, spinal cord, skeleton, sciatic nerves, pancreas, stomach-intestines, liver, and uterus show a definite increase in weight.
2. The heart, brain, and lungs remain nearly constant in weight.
3. The thymus, ovaries, parotid and submaxillary glands, spleen, testes, epididymides, and thyroid suffer more or less well-marked decrease in weight.

The growth tendencies of the various organs in the young rats during the thirst experiments correspond in general to those found in rats of similar age during underfeeding, although certain exceptions occur (testes and kidneys).

Likewise the results of the thirst tests (also those of the inanition experiments) show a general resemblance to those of similar character in adults. There are certain differences according to age, however, as well as according to the type of inanition employed.

LITERATURE CITED

ARON, HANS 1911 Nutrition and growth. Philippine Jour. Science, vol. 6.

DONALDSON, H. H. 1911 The effect of underfeeding on the percentage of water, on the ether-alcohol extract, and on the medullation in the central nervous system of the albino rat. Jour. Comp. Neur., vol. 21, no. 2.
1915 The rat. Reference tables and data. Memoirs of The Wistar Institute of Anatomy, no. 6. Phila.

DONALDSON, H. H., AND CONROW, SARA B. 1919 Quantitative studies on the growth of the skeleton of the albino rat. Am. Jour. Anat., vol. 26, pp. 237–314.

HATAI, S. 1904 The effect of partial starvation on the brain of the white rat. Am. Jour. Physiol., vol. 12, no. 1.
1913 On the weights of the abdominal and the thoracic viscera, the sex glands, ductless glands and the eyeballs of the albino rat (Mus norvegicus albinus) according to body-weight. Am. Jour. Anat., vol. 15, no. 1.
1914 On the weight of the thyums gland of the albino rat (Mus norvegicus albinus) according to age. Am. Jour. Anat., vol. 16, no. 2.

Hatai, S. 1915 The growth of the body and organs in albino rats fed with a lipoid-free ration. Anat. Rec., vol. 9, no. 1.

1918 On the weight of the epididymis, pancreas, stomach and of the submaxillary glands of the albino rat (Mus norvegicus albinus) according to body weight. Am. Jour. Anat., vol. 24, no. 1.

Jackson, C. M. 1913 Postnatal growth and variability of the body and of the various organs in the albino rat. Am. Jour. Anat., vol. 15, no. 1.

1915 Effect of acute and chronic inanition upon the relative weights of the various organs and systems of adult albino rats. Am. Jour. Anat., vol. 18, no. 1.

1915 a Changes in the relative weights of the various parts, systems and organs of young albino rats held at constant body-weight by underfeeding for various periods. Jour. Exp. Zoöl., vol. 19, no. 2.

Jackson, C. M., and Stewart, C. A. 1920 The effects of inanition in the young upon the ultimate size of the body and of the various organs in the albino rat. Jour. Exp. Zoöl., vol. 30, no. 1.

Kudo, T. 1921 Studies on the effect of thirst. I. Effects of thirst on the weights of the various organs and systems of adult albino rats. Am. Jour. Anat., vol. 28, no. 2.

McCarrison, R. 1919 The pathogenesis of deficiency disease. VIII. The general effects of deficient dietaries on monkeys. Indian Jour. Med. Research, vol. 7, no. 2 (Oct.).

Meyer, L. F. 1913 Ueber den Wasserbedarf des Säuglings. Zeitschr. f. Kinderheilk., Bd. 5, S. 1–30.

Stewart, C. A. 1918 Changes in the relative weights of the various parts, systems and organs of young albino rats underfed for various periods. Jour. Exp. Zoöl., vol. 25.

1919 Changes in the weights of the various parts, systems and organs in albino rats kept at birth-weight by underfeeding for various periods. Am. Jour. Physiol., vol. 48.

Variot et Lassabliere 1909 Autonomie du développement de l'encéphale dans les jeunes enfants. C. R. Soc. Biol., Paris, T. 66.

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STUDIES ON THE MAMMARY GLAND

VII. THE DISTRIBUTION OF THE SUBCUTANEOUS FAT AND ITS RELATION TO THE DEVELOPING MAMMARY GLANDS IN MALE AND FEMALE ALBINO RATS FROM BIRTH TO TEN WEEKS OF AGE

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THREE FIGURES

While fixing the glands for fat stains in the study of witches' milk (Myers, '19), it was noticed that when the entire skin of an albino rat was removed, stretched out on cork, and placed in Flemming's fluid for a short time, the subcutaneous fat was beautifully differentiated from the surrounding tissues. There seemed to be a constant relation between the deposit of subcutaneous fat and the development of the mammary glands. Hence the present work was undertaken to determine this relation.

MATERIAL AND TECHNIQUE

Representative stages from birth to ten weeks were selected from apparently healthy albino rats of normal body weight. For each stage a male and a female from the same litter and of approximately the same body weight were studied and compared. The rats were killed by chloroform and an incision was made extending from the dorsal part of the root of the tail along the spines of the vertebrae and over the skull to the tip of the nose. The skin was then reflected, special precautions being used to remove all the subcutaneous fat with the skin. The skin was then stretched out on a piece of cork with the inner surface up, after which it was placed either in Flemming's fluid or 1 per cent osmic-acid solution. The preparations were left here until the subcutaneous fat had become dark brown. This usually required thirty minutes to one hour. They were then washed in running water for an hour or so and carried through the various grades of alcohol. It was noticed that in skins left much longer than one hour the epidermis became somewhat darkened so that the subcutaneous fat was no longer so sharply outlined. After the material was hardened in the alcohol, drawings were made of the entire skin with the subcutaneous fat represented in black, the position of each of the twelve nipples being indicated on the drawing. These preparations did not show the ramifications of the milk ducts, hence it became necessary to remove the osmic-acid stain and make a study of the relation of the ducts to the fat. First, the connective-tissue layer of the skin was removed according to the method employed in an earlier work (Myers, '16). This thin layer, which contained the fat and milk ducts, was placed in a weak solution of hydrogen peroxide until the osmic-acid stain had entirely disappeared. It was then stained in very much diluted Delafield's hematoxylin and cleared according to the method described by Lane-Claypon and Starling ('06). These cleared preparations were then projected onto the original drawings in such a manner that the nipples coincided with the points indicating their position on the original drawing. This made it possible to outline the general distribution of each gland, thus showing the relation of the milk ducts to the subcutaneous fat.

Since osmic acid stains only the unsaturated neutral fat, triolein, the findings with osmic acid were verified by staining gross specimens with sudan III or scarlet red.

As soon as the skin was removed from the body of the animal, the entire body was placed in 1 per cent osmic acid to make sure that all subcutaneous fat had been removed. In most cases very little or no fat was left on the body wall of the animal.

In another series of animals the subcutaneous tissue was left on the body wall when the skin was removed. These bodies were then placed in osmic acid, scarlet red or sudan III, and the fat studied in its normal position. The results were similar to those with the other methods.

Microscopic sections were made through certain regions in order to verify the observations made upon the preparations stained in toto. Some of these sections were made from tissues fixed in Flemming's fluid. Frozen sections made from each stage studied were stained in sudan III or scarlet red and counterstained in hematoxylin.

OBSERVATIONS

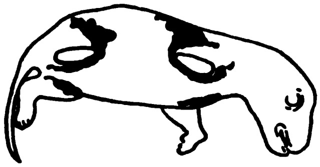
The stains employed failed to reveal any subcutaneous fat in gross preparations from animals killed immediately after birth. In specimens taken *six to ten hours after birth,* however, a considerable amount of fat is seen deposited in the subcutaneous tissue. This fat is not uniformly distributed. In gross specimens this subcutaneous fat does not appear in solid masses at this stage, but appears somewhat granular. In a general way it may be said that the fat is deposited in the area supplied by the larger arteries and their branches. Therefore, one finds fat deposited more abundantly in the inguinal region around the inferior epigastric artery and its rami and in the thoracic and upper abdominal regions around the superior epigastric and mammary and intercostal arteries. In the region of the ventral midline, and for some distance to the side of this line, no fat appears. In the midabdominal region where the superior and inferior epigastric branches become very small, fat is not deposited at this stage. The relation of this early fat deposit to the blood-vessels is very constant. Along the larger branches the fat is quite plentiful, but it gradually disappears as one passes along the rami of these branches.

The nipple of the abdominal mammary gland lies medial to the fat being deposited in the inguinal and lower abdominal regions. Its primary duct, however, passes caudolaterally and divides into two or three branches which enter the region of the depositing fat. Here these branches subdivide, and all the terminal ramifications of the abdominal gland are found in the fat deposit. The first and second inguinal glands lie medial to the posterior continuation of the region in which fat is being deposited. The terminal branches of their ducts, however, ramify in this fat.

In the cervical region is an area in which fat is being deposited that extends somewhat cephalad and laterad from the root of the neck. There is some indication of small strands of fat connecting this area with the thoracic area which extends caudad very nearly to the costal margin and dorsad where it closely approaches the midline of the back. The nipple of the first thoracic gland lies medial to the axillary region, and fat is being deposited between this nipple and the axilla. The primary milk duct from this gland passes cephalad where it enters, and its rami terminate around the fat being deposited. The second and third thoracic nipples lie medial to the fat being laid down in the thoracic region. The branches of these glands also terminate around this fat.

Thirty hours after birth the subcutaneous fat is present in greater quantities and extends over larger areas than in the preceding stage (fig. 1). In the inguinal and lower abdominal region the deposit of fat is so sharply outlined that it may be designated as the inguinal fat pad. This pad of fat on each side extends from a position anterior to the posterior portion of the crest of the ilium toward the midventral line. Before reaching this line, however, it turns caudad, passes over the pubis, and extends nearly to the anal region. That pad of fat in the region of the iliac crest has become so thick, and yet is so unevenly distributed, that in gross stained preparations transmitted light penetrates only in certain areas. However, as one passes toward the pubic region and caudad to this, one observes the fat in smaller amounts so that it has somewhat of a granular appearance. Extending from the pubic portion of this fat pad may be seen thin narrow strands of fat extending cephalomedially to a point near the umbilicus. At this stage the inguinal fat pads of the opposite sides are not connected. The inguinal fat pad does not extend medially as far as the abdominal nipple. In case of the first and second inguinal nipples, however, this pad of fat has extended very nearly to their lateral margin.

Cephalad to the inguinal fat pad is a considerable area of subcutaneous tissue which in the previous stage contains no visible fat. However, at this stage one sees an occasional very



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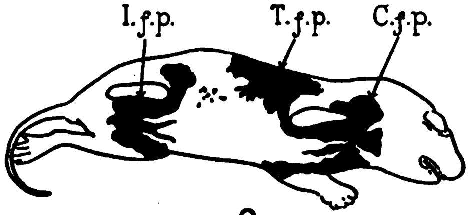

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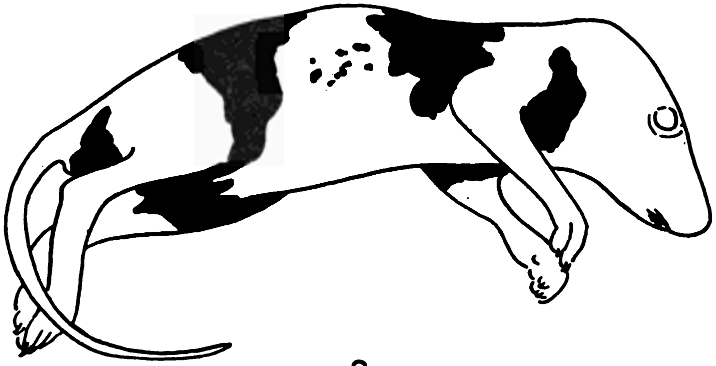

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Fig. 1 shows the distribution of subcutaneous fat in an albino rat thirty hours after birth.

Fig. 2 shows the distribution of subcutaneous fat in an albino rat five days after birth. *C.f.p.*, cervical fat pad; *T.f.p.*, thoracic fat pad; *I.f.p.*, inguinal fat pad.

Fig. 3 shows the distribution of subcutaneous fat in an albino rat three weeks after birth.

small mass of fat in close relation to a blood vessel. As the thoracic region is approached, the subcutaneous fat is seen deposited in considerable amounts. In fact, one may now describe a thoracic fat pad. However, its boundaries are not so sharp as those of the inguinal fat pad. This is particularly true of the caudal boundary. The caudal boundary of the thoracic fat pad extends from a position very near the dorsal midline ventrally along and slightly below the costal margin. The medial boundary lies a few millimeters from the ventral midline, while the cephalic boundary passes just caudad to the axilla. This fat pad had increased in size so that its medial margin approaches very closely the lateral margin of the base of the nipples of the second and third thoracic glands.

The mass of fat being deposited in the cervical region in the previous stage has become quite definite in outline, and from this time will be designated the cervical fat pad. It extends from the anterior portion of the axilla into the root of the neck, where it turns laterodorsad and extends to the laterodorsal side of the neck. Caudally this pad of fat connects with the thoracic pad by means of narrow strands. The nipple of the first thoracic gland lies at the caudal end of the cervical fat pad, and its base is partly surrounded by this fat. The ducts of this gland ramify in the cervical fat pad.

Fifty-two hours after birth the fat pads are more distinct than in previous stages. They have not only thickened considerably, but extend over somewhat larger areas. The inguinal fat pads are slightly connected at their posterior ends. The cervical fat pads are also connected by small strands that extend across the midline. The inguinal fat pad has extended toward the midline until the nipples of the first and second inguinal glands are nearly surrounded by fat. The nipple of the abdominal gland still lies slightly medial to this pad. The strand of fat which in the previous stage extended from the pubic region to the region of the umbilicus has become more prominent. In the preceding stage attention was called to the fact that in the subcutaneous tissue lying between inguinal and thoracic fat pads an occasional small isolated mass of fat was observed. In the present stage such masses of fat are more numerous.

In the case of the nipples of the second and third thoracic glands somewhat isolated masses of fat may now be seen lying medial to their bases. The nipple of the first thoracic gland is so completely surrounded by fat that one is unable to see the position of the nipple in stained preparations. The cervical fat pads are slightly connected across the midline.

Five days after birth (fig. 2) the view of the bases of all the nipples except the abdominal, when examined from the inner surface of the skins, is completely obscured by the dense deposit of subcutaneous fat. In other words, the fat pads have extended toward the midline sufficiently to completely surround and cover up the bases of the nipples. In case of the nipple of the abdominal gland, the fat very closely approaches the lateral side of its base. The isolated masses of subcutaneous fat between the inguinal and thoracic pads have increased considerably in size. However, there is no direct fatty connection between these two pads at this stage. The cervical pads are now connected by good-sized masses of fat.

At the *end of the first week* the fat pads do not differ from the previous stage, except that they have become much thickened and slightly more extensive. The masses of fat between the thoracic and inguinal pads have increased in size so that in some specimens a few of them have fused to form a narrow connection between these two pads.

From the beginning of the *second week to the tenth week* (fig. 3) the subcutaneous fat pads increase in size with the general growth of the animal. They also vary somewhat in size depending upon the animal's health and food supply. During this period strands of fat may be observed extending across the midline connecting the cervical fat pads of opposite sides. Similar strands appear in the perineal region connecting the caudal portions of the right and left inguinal fat pads.

The milk ducts about the time of puberty undergo marked proliferation (Myers, '16) and it is interesting to note that their ramifications follow for the most part the same course of distribution as the subcutaneous fat followed at an earlier stage. Thus at this time milk ducts of the opposite sides cross the midline in both the cervical and perineal regions and ramify in the fat already deposited in these regions. Other ducts send out branches which ramify in the processes of fat extending from the inguinal fat pads to the region of the umbilicus. Although strands of fat connect the thoracic and inguinal fat pads on each side, no ducts have been observed to ramify in these strands; so there is a definite interval existing between the ducts of the third thoracic gland and the abdominal gland on each side.

The ducts of the mammary glands of male rats after the fifth week do not grow as fast as those of females (Myers, '17), but no corresponding difference between the series was observed in the deposit of subcutaneous fat. The males at all ages show deposits similar to those of the females.

DISCUSSION

We believe neutral fat is deposited in the subcutaneous tissue for at least two purposes: first, as a protection against cold; second, as a reserve supply of food and energy. According to Berg ('11), much fat is deposited in the subcutaneous tissue of the new-born child. The question arises as to why so little or no subcutaneous fat is present in the rat at birth. In the first place, this animal is born in a very immature stage. Being born, however, without any special mechanism against cold, neutral fat begins to deposit beneath the skin very soon.

Again one might ask why this subcutaneous fat is not distributed more uniformly over the body. To be of much value as a protection against cold, one would expect to find a fairly uniform layer of subcutaneous fat as in some other animals. The answer to this may be found in the fact that the rat develops a fairly heavy coat of hair quite early in life, hence there is not much need for a further protective layer of fat. Moreover, the habitat of the animal may have some influence on the need of a protective layer of fat. For example, the rat usually inhabits fairly warm places, such as houses and cellars. It further protects itself by burrowing.

Attention has been called to the fact that the first subcutaneous fat is deposited in the neighborhood of the branches of the milk ducts. Next, fat is laid down in greatest quantities in regions which will later be occupied by milk ducts. For example, the fat pads, at first small, become extended over a slightly larger area than the ducts will occupy during pregnancy and lactation. It was pointed out (Myers, '16) that the first cervical glands slightly before or at the age of puberty send branches across the midline so as to establish at least a gross continuity between the glandular tissue on one side with that of the opposite side. The same was true in case of the branches of the second inguinal glands. In both of these positions we see fat extending across the midline during the first week. In no other position at any time before puberty does fat extend across the midline.

Why should subcutaneous fat be deposited in definite pads in regions where the milk ducts later ramify? Is it because fat is a good medium for the ducts to proliferate in, or does it have some special rôle to play in the later functional stages of the milk ducts during pregnancy and lactation?

While studying the effects of inanition on the developing mammary glands (Myers, '19), it was observed that the subcutaneous fat that appears very early in the neighborhood of the milk ducts soon becomes greatly decreased after the amount of food is reduced to a minimum. In those animals that were underfed from birth very little subcutaneous fat was deposited. Along with this scanty deposit of subcutaneous fat occurs a partial failure of development on the part of the milk ducts.

LITERATURE CITED

BERG, W. 1911 Ueber die Anlage und Entwickelung des Fettgewebes beim Menschen. Zeitschr. f. Morph. u. Anthrop., Bd. 13, S. 305–342.

MYERS, J. A. 1916 Studies on the mammary gland. I. The growth and distribution of the milk ducts and the development of the nipple in the albino rat from birth to ten weeks of age. Am. Jour. Anat., vol. 19, pp. 353–389.

1917 Studies on the mammary gland. II. The fetal development of the mammary gland in the female albino rat. Am. Jour. Anat., vol. 22, pp.195–223.

1917 a Studies on the mammary gland. III. A comparison of the developing mammary glands in male and female albino rats from the late fetal stages to ten weeks of age. Anat. Rec., vol. 13, pp. 205–226.

1919 The histology of the mammary gland in the male and female albino rat from birth to ten weeks of age. Am. Jour. Anat., vol. 25, pp. 395–435.

1919 a Studies on the mammary gland. V. The effects of inanition on the mammary gland in male and female albino rats from birth to ten weeks of age. Am. J. Dis. Child. (May), vol. 17, pp. 311–328.

1919 b Studies on the mammary gland. VI. The development of mammary gland from its earliest appearance until the period of pregnancy. Am. J. Dis. Child. (July), vol. 18, pp. 4–13.

A Contribution to the Topographic Anatomy of the Thymus Gland, with Particular Reference to its Changes at Birth and in the Period of the New-Born

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MINNEAPOLIS

A CONTRIBUTION TO THE TOPOGRAPHIC ANATOMY OF THE THYMUS GLAND, WITH PARTICULAR REFERENCE TO ITS CHANGES AT BIRTH AND IN THE PERIOD OF THE NEW-BORN

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The peculiar life history of the thymus gland in man is reflected in its topography, which is modified from time to time by different phases of its growth and involution and by changes in the neighboring structures and viscera. These changes in thymus topography begin during fetal life and are particularly striking at birth when the chest and its contained organs are greatly modified as respiration is established. The natal changes of the thymus have received comparatively little study, and the lack of information on this subject seems to have led to considerable confusion regarding the normal form and extent of the organ in early postnatal life. The following account is an attempt to trace in detail these early modifications in thymus topography with particular reference to the normal or usual conformation and relations of the structure in early infancy. This work was done in the Department of Anatomy of the University of Minnesota under the direction of Dr. R. E. Scammon.

I. MATERIAL AND METHODS

The material used in this study consisted of sixty-five fetuses and full-term children. The specimens ranged from 10 to 55 cm. in crown-heel or total length. Most of these form a part of the collection of the Institute of Anatomy of the University of Minnesota. Twenty-five of the infants were stillborn and twenty were children in whom respiration had been at least partially established. Fifty-seven were preserved by intravascular injection of an aqueous solution of 10 per cent. liquor formaldehydi and 1 per cent. chromic acid, one was sectioned serially, and 7 were observed at the necropsy.

Following the suggestion of Hammar[1] that only thymus glands obtained from healthy individuals should be used in the study of this organ, no material was used in which pathologic conditions were macroscopically observable.

This material was studied by means of dissections, graphic reconstructions and freehand sections. The dissection of the first forty-two subjects in the series was made in the following manner; the skin, subcutaneous tissues, muscles, etc., were reflected from the anterior thoracic wall and the cervical region as far superiorly as the inferior border of the mandible. Next, the sternocleidomastoid and the infrahyoid muscles were removed and the part of the thymus extending above the sternal notch was measured with dividers. The ribs and clavicles were then cut at the anterior axillary lines, elevated and separated from their connections with underlying structures. In this manner the larynx, thyroid, thymus, pericardium, lungs, larger vessels, etc., of the mediastinum and cervical regions were exposed.

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[1] Hammar, J. A.: Fünfzig Jahre Thymusforschung, Ergeb. Anat. u. Entwicke **19**: Pt. I, 274, 1909.

All measurements of these various structures as shown on the drawings were made with fine pointed dividers and were plotted on coordinate paper in the form of outline drawings of which several are reproduced in Figures 1 to 12 inclusive. Figures 19 to 24 inclusive were drawn from plottings of the anterior dissections which were made by the use of the graphic reconstruction apparatus designed by Scammon.[2] Fifteen specimens (Cases 43 to 58 inclusive, except Case 56) were cross sections prepared by sectioning the specimens free hand with a heavy, sharp knife. Figures 37 to 42 inclusive are drawings of selected specimens of this series. The 7 necropsies, which are included in the series (Cases 59 to 65 inclusive) did not afford ideal conditions for this work. However, measurements of these specimens were made with the dividers while the organs were in situ and the thymus glands carefully removed and placed on cotton pads in hardening fluid. The form was thus preserved, and the specimens were then drawn to standard size. These are shown in Figures 31 to 36 inclusive.

The following observations were made on each specimen:

(a) The location of the thymus, whether completely in the thorax or partly in the thorax and extending into the cervical region. This classification of location is that suggested by Coplin.[3]

(b) The lobation of the thymus, i.e., number of lobes observable macroscopically. This classification also follows Coplin.[3]

(c) The overlapping of the thymus on the right ventricle, i.e., to what extent, if any, the right or left portions of the thymus extended on this part of the heart.

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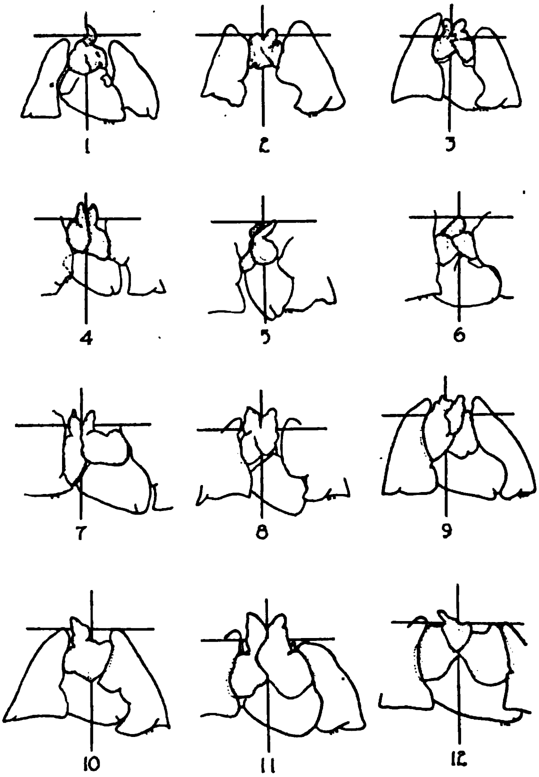
[2] Scammon, R. E.: A Simple Method of Graphic Reconstruction, Anat. Rec. **21**:552, 1921.

[3] Coplin, W. M. L.: Morphology of the Human Thymus. Pub. Jefferson Medical College and Hospital, **1**:116, 1915. Coplin suggests four different types of thymus glands in regard to lobation. He describes unilobar, bilobar, and trilobar glands which have respectively one, two or three lobes. Thymus glands in which division into lobes is imperfectly marked or in which fusion is so complete that no semblance of lobar distinction can be made out are classified as conglomerate. He found no thymus glands located entirely in the cervical region. I have likewise found none of this type in his material. A thoracic thymus is defined by Coplin as one of which the summit, under ordinary respiratory conditions, does not rise above the upper margin of the sternum. Cervicothoracic thymus glands are those of which continuous parts lie in the thorax and extend upward into the neck.



Figs. 1 to 12 represent outline drawings, plotted to scale, of a number of dissections in situ of thymus glands of fetuses and new-born children. None of these specimens had breathed.

Fig. 1.—Fetus 226 mm. in length (No. 12).
Fig. 2.—Fetus 234 mm. in length (No. 13).
Fig. 3.—Fetus 243 mm. in length (No. 15).
Fig. 4.—Fetus 245 mm. in length (No. 16).
Fig. 5.—Fetus 283 mm. in length (No. 18).
Fig. 6.—Fetus 235 mm. in length (No. 14).
Fig. 7.—Fetus 253 mm. in length (No. 17).
Fig. 8.—Fetus 374 mm. in length (No. 29).
Fig. 9.—Fetus 308 mm. in length (No. 22).
Fig. 10.—Fetus 300 mm. in length (No. 21).
Fig. 11.—Fetus 331 mm. in length (No. 25).
Fig. 12.—Fetus 384 mm. in length (No. 30).

(d) The overlapping of the thymus by the lungs, i.e., to what extent, if any, either or both lungs lay anterior to the thymus.

(e) The form of the thymus, i.e., whether the outline of the thymus was broad or elongate. A "broad" thymus was defined as one whose transverse diameter was equal to or greater than its craniocaudal diameter, and an "elongate" thymus as one whose craniocaudal diameter was greater than its transverse diameter.[4]

(f) Condition of the lungs in relation to respiration. The decision as to whether or not an individual had breathed was based on the floating test as well as on a careful examination of the lobules and the appearance of the anterior borders of the lungs with the hand lens. Lungs in which breathing has occurred show distinct characteristics when compared with those of the fetus or stillborn. The anterior border and antero-inferior angles of the former have lost their sharp edges and have become rounded. The lobules on the surface are larger, more distinct and of higher color. On section, the lungs in which respiration has begun appear spongy, and on pressure emit a frothy fluid containing numerous fine air bubbles. The latter phenomenon is noted in material which has been preserved for months as well as in fresh specimens. The extent and order of expansion of the parts of the lungs followed the observations of Champneys,[5] except that he found that the antero-inferior borders were often unexpanded.

II. SUMMARY OF OBSERVATIONS

The data secured by the methods described above are summarized in Tables 1, 2 and 3. Since the series is arranged according to the crown-heel length of the specimens, one may quickly discern the changes occurring in any type of observation in relation to increase in body length and consequent age. Furthermore, the relation of the establishment of respiration to the various features observed may be noted by following the column allotted to the record of whether or not an individual had breathed. In the following analysis of these data the material will first be considered in toto and then as arranged in two series on the basis of the establishment or nonestablishment of respiration.

A. *Analysis of entire series of cases.*—A tabulation of the data obtained from the entire series of cases is shown in Table 1, and the following summary of the several observations is made from it.

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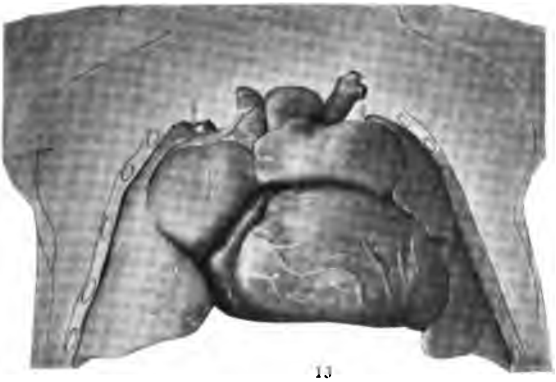
[4] A few thymus glands, because of their great lateral extension inferiorly, were classified as "broad" even though their craniocaudal diameters were a little greater than their transverse diameters—the former being due to the presence of slender cervical processes of some length.

[5] Champneys, F. H.: Artificial Respiration in Stillborn Children, Med.-Chir. Tr. Lond. **64**:41, 1881.



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Figs. 13 to 18 represent a series of dissections of chests of new-born children illustrating the changes in the form of the thymus coincident with the establishment of respiration.

Fig. 13.—Anterior dissection of the thorax of a new-born which had breathed (No. 39, 485,mm. long). The thymus is still of the fetal type though it evidently was already compressed, as is shown by the cervical portion being forced against the thyroid gland. This cervical portion was 7 mm. in thickness.

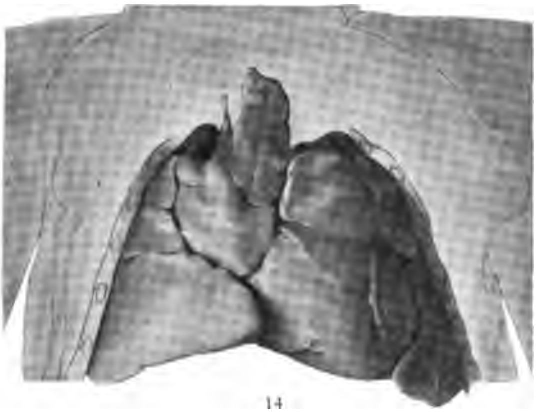

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Fig. 14.—Anterior dissection of the thorax of a new-born which had breathed (No. 40, 501 mm. long). The cervical portion of the thymus extended to the thyroid against which it was pressed, and then projected anteriorly. The anterior border of the right lung and the anterior-inferior angles of both lungs show the characteristic thickening in these areas in the earliest stages in the establishment of respiration.

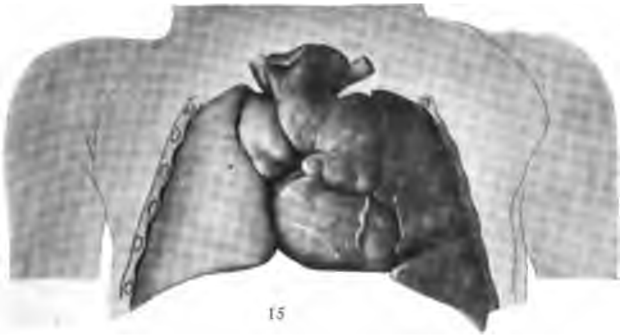

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Fig. 15.—Anterior dissection of the thorax of a premature new-born (No. 31, 402 mm. long) which had breathed. The thymus has a very wide cervical portion which extended to the inferior border of the thyroid gland against which it was compressed.

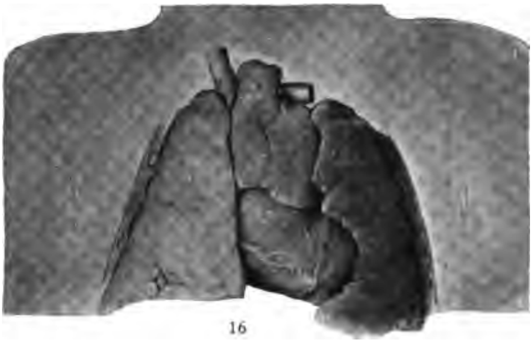

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Fig. 16.—Anterior dissection of the thorax of a premature new-born (No. 29, 374 mm. long) which had breathed. The thymus extended so far posteriorly that it compressed the innominate artery, trachea and esophagus. The thymus is markedly compressed from side to side, and the lobules of the lungs, anteriorly, are very marked. Figure 45 is of this specimen after the anterior half of the thymus was dissected away.

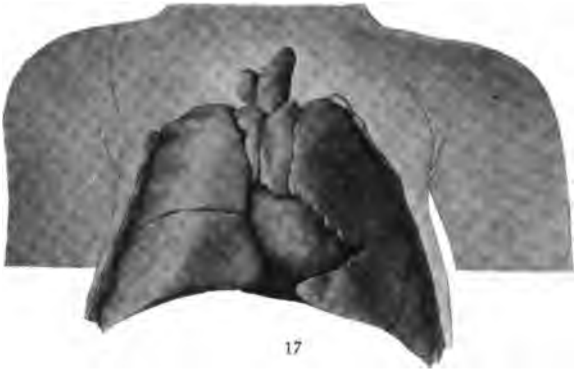

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Fig. 17.—Anterior dissection of the thorax of a premature new-born (No. 32, 412 mm. long) which had breathed. The cervical portion is quite large, and extends to the thyroid. The inferiormedial angles of the lungs have extended almost to the midline—the right lung practically reaching it.

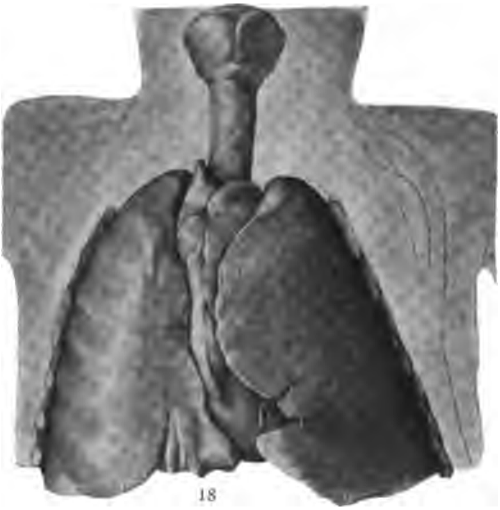

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Fig. 18.—Anterior dissection of the thorax of a newborn (No. 41, 510 mm. long) which had evidently breathed longer than any other in the series. The thymus is markedly compressed, the right lung has crossed the midline, and the left in its middle region has reached it. The thymus does not extend far into the cervical region, but it does extend very far down on the right ventricle. It is, like all the others, marked by a groove where it was in contact with the superior border of the manubrium sterni. Posteriorly, it compressed the aortic arch, innominate artery and trachea.

The predominating location of the thymus is cervicothoracic, this position being found in fifty-one cases, or 82.2 per cent. The thoracic location was found in eleven cases, or 17.8 per cent. The bilobed type of thymus predominates, with a total of thirty-nine cases, or 62.9 per cent. The conglomerate, trilobed, and unilobed thymus follow in frequency; the conglomerate with ten cases, or 16.1 per cent., the trilobed with seven cases, or 11.1 per cent., and the unilobed with six cases, or 9.9 per cent. The thymus was overlapped by the right lung in twenty cases, or 32.2 per cent., and by the left lung in eighteen cases, or 29 per cent. The right portion of the thymus overlapped the right ventricle in ten cases, or 16.1 per cent., and the left portion of the organ overlapped the right ventricle in seventeen cases, or 27.3 per cent. A broad thymus was present in forty-one cases, or 66.2 per cent., and an elongate thymus in twenty-one cases, or 33.8 per cent. The above figures are for the entire series and, therefore, include the individuals that have not breathed as well as those who have breathed.

B. *Analysis of cases in which respiration had not been established.* —When the individuals who have not breathed are considered as a separate group (Table 2) the following results are obtained.

The most frequent location of the thymus is cervicothoracic, with a total of thirty-six cases, or 80 per cent. The bilobed thymus is the most common in this group, forming 57.8 per cent. of the total number. The conglomerate type ranks next with nine cases, or 20 per cent., the unilobular numbers six cases, or 13.4 per cent., and the trilobed is least numerous, being represented by only four cases, or 8.8 per cent. The thymus is overlapped by the right lung in but three cases, or 6.6 per cent., and by the left lung in only two cases, or 4.4 per cent.

These figures indicate that in the nonbreathing individuals there is practically no overlapping of the thymus by the lungs. In no case in the nonbreathing group did the right portion of the thymus extend over the right ventricle of the heart, and the left portion projected on the right ventricle in only two cases, or 4.4 per cent. The broad type of thymus predominates in the nonbreathing group, with a total of thirty-seven cases, or 82.3 per cent. The elongate type occurs in only eight cases, or 17.7 per cent.

The individuals who have not breathed were also arranged into two subgroups according to total body length (Table 2). The first subgroup included all specimens of 30 cm. or less and contains twenty-one cases. The second subgroup includes all cases above 30 cm. and contains twenty-four cases. The lobation in both these groups is similar to the whole nonbreathing series, i.e., predominantly bilobed. The thoracic thymus is slightly more common in the second group. This may be interpreted as representing a stage in the migration of the thymus from its embryonic position in the cervical region to its final

TABLE 1.—TABULATION OF THE SEVERAL OBSERVATIONS MADE ON THE ENTIRE SERIES OF THYMUS GLANDS. NOS. 1 TO 42, INCLUSIVE, WERE DISSECTIONS; NOS. 43 TO 58, INCLUSIVE, WERE TRANSVERSE SECTIONS, AND NOS. 59 TO 65 WERE NECROPSIES

Series Number	Standing Height	Sex	Type of Thymus	Lobation of Thymus	Lungs Overlap Thymus		Thymus Extend on Ventricle		Form of Thymus	Breathed
					Right	Left	Right	Left		
1	100	F	C-T	Cong.	—	—	—	—	B	—
2	119	M	C-T	Bi.	—	—	—	—	E	—
3	123	F	Th.	Uni.	—	—	—	—	E	—
4	133	F	C-T	Bi.	—	—	—	—	E	—
5	143	M	Th.	Cong.	—	—	—	—	B	—
6	186	F	C-T	Uni.	—	—	—	—	E	—
7	200	F	C-T	Bi.	—	—	—	—	E	—
8	220	F	C-T	Bi.	—	—	—	—	B	—
9	223	F	C-T	Bi.	—	—	—	—	B	—
10	223	M	C-T	Tri.	—	—	—	—	E	—
11	224	F	C-T	Bi.	—	—	—	—	B	—
12	226	M	C-T	Cong.	—	—	—	—	B	—
13	234	F	C-T	Cong.	—	—	—	—	B	—
14	235	M	Th.	Tri.	—	—	—	—	B	—
15	243	F	C-T	Bi.	—	—	—	—	B	—
16	245	M	C-T	Bi.	—	—	—	—	B	—
17	253	F	C-T	Bi.	—	—	—	—	B	—
18	283	M	C-T	Bi.	—	—	—	—	E	—
19	283	F	C-T	Bi.	—	—	—	—	E	—
20	295	F	C-T	Tri.	—	—	—	—	B	—
21	300	F	C-T	Uni-	—	—	—	—	B	—
22	308	F	C-T	Cong.	—	—	—	—	B	—
23	313	F	C-T	Cong.	—	—	—	—	B	—
24	325	M	C-T	Bi.	—	—	—	—	B	—
25	331	F	C-T	Bi.	—	—	—	+	B	—
26	332	M	C-T	Bi.	—	—	—	—	B	—
27	337	F	C-T	Bi.	—	—	—	+	B	—
28	364	F	C-T	Cong.	+	+	—	+	B	—
29	374	F	C-T	Tri.	+	+	+	+	E*	+
30	384	F	C-T	Tri.	—	—	—	+	B	—
31	402	F	C-T	Tri.	+	+	+	+	B†	+
32	412	F	C-T	Bi.	+	+	+	+	E	+
33	421	M	C-T	Cong.	+	+	+	+	E†	+
34	402	F	C-T	Bi.	+	+	+	+	E*†	+
35	433	F	C-T	Cong.	—	—	—	—	B	—
36	448	F	Th.	Bi.	—	—	—	—	B	—
37	453	F	C-T	Bi.	—	—	—	—	B	—
38	470	F	Th.	Bi.	+	+	—	—	B*	+
39	485	M	C-T	Bi.	+	—	—	+	B*	—
40	501	F	C-T	Tri.	+	+	+	+	B*†	+
41	510	F	C-T	Bi.	+	+	+	+	E*	+
42	516	F	C-T	Cong.	—	—	—	—	B	—
43	295	F	C-T	Uni.	—	—	—	—	B	—
44	310	F	C-T	Bi.	+	+	—	+	E	+
45	320	M	C-T	Bi.	—	—	—	—	B	—
46	340	F	Th.	Bi.	—	—	—	—	B	—
47	360	F	C-T	Bi.	—	—	—	+	B	—
48	370	M	C-T	Bi.	—	—	—	—	B	—
49	373	M	Th.	Bi.	—	—	—	—	B	—
50	375	F	C-T	Bi.	+	+	—	—	E	+
51	380	M	C-T	Bi.	+	+	+	+	E	+
52	380	F	C-T	Bi.	+	+	+	+	E	+
53	382	M	C-T	Bi.	+	+	+	+	E	+
54	410	M	C-T	Bi.	—	—	—	—	B	—
55	420	F	C-T	Bi.	—	—	—	—	B	—
56	430	F	C-T	Bi.	+	—	—	—	E	+
57	480	M	Th.	Uni.	—	—	—	—	B	—
58	510	F	Th.	Bi.	—	—	—	—	B	—
59	370	F	C-T	Bi.	+	+	—	—	B	+
60	515	F	C-T	Bi.	—	—	—	—	B	—
61	305	F	C-T	Bi.	+	+	—	+	E	+
62	450	M	Th.	Bi.	+	+	—	+	E	+
63	14 mo.	F	Th.	Bi.	+	+	+	+	E	+
64	510	M	C-T	Bi.	+	+	+	—	B	+
65	550	F	C-T	Cong.	+	+	+	—	E	+

* Constriction or flattening of structures posterior to thymus.
† Cervical part of thymus very large.

position in the thorax in postnatal life.[6] There is no overlapping of the thymus by the lungs in the first group, and but a few instances of slight overlapping in the second group which are probably due to the inclusion of a few individuals suspected of having breathed slightly. The thymus in no case in the first group extends on either side on the right ventricle. In the second group the thymus in a few cases extends on the left ventricle; this is probably due to slight breathing. Less than two-thirds of the cases in the first group have the broad type of thymus, whereas every case in the second group has the broad thymus.

TABLE 2.—CONDITION OF THE THYMUS IN INDIVIDUALS WHICH HAVE NOT BREATHED

	Specimens 100 to 300 Mm. in Length (21 Cases)		Specimens 300 to 315 Mm. in Length (24 Cases)	
	Number	Per Cent.	Number	Per Cent.
Lobation of Thymus				
Unilobar	3	14.3	2	8.3
Bilobar	11	52.4	16	66.7
Trilobar	3	14.3	1	4.1
Conglomerate	4	19.0	5	20.9
Position of Thymus				
Cervicothoracic	18	85.7	19	79.1
Thoracic	3	14.3	5	20.9
Lungs Overlap Thymus				
Right side	0	0.0	2	8.4
Left side	0	0.0	1	4.2
Thymus Extends on Ventricle				
Right side	0	0.0	1	4.2
Left side	0	0.0	4	16.7
Form of Thymus				
Broad	13	61.9	24	100.0
Elongate	8	38.1	6	0.0

TABLE 3.—EFFECT OF THE ESTABLISHMENT OF RESPIRATION ON THE THYMUS

	Individuals Which Have Not Breathed		Individuals Which Have Breathed	
	Number	Per Cent.	Number	Per Cent.
Position of Thymus				
Cervicothoracic	36	80.0	16	80.0
Thoracic	9	20.0	4	20.0
Lobation of Thymus				
Unilobar	6	13.4	0	0.0
Bilobar	26	57.8	15	75.0
Trilobar	4	8.8	3	15.0
Conglomerate	9	20.0	2	10.0
Lungs Overlap Thymus				
Right side	3	6.6	20	100.0
Left side	2	4.4	16	80.0
Thymus Extends on Ventricle				
Right side	0	0.0	13	65.0
Left side	2	4.4	16	80.0
Form of Thymus				
Broad	37	82.3	5	25.0
Elongate	8	17.7	15	75.0

C. *Analysis of cases in which respiration was partially or wholly established.*—The findings regarding the thymus in the group of cases in which respiration was partially or wholly established are given in Table 3.

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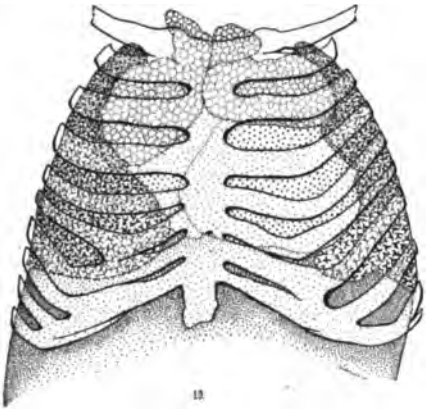
[6] Canelli, H. K.: Contributo allo studio anatomico e pathologico dell timo nella prima eta, Pediatria **28**:753, 1920.

The most common position of the thymus in individuals who have breathed, as in the entire series, is the cervicothoracic with a total of sixteen cases, or 80 per cent. The thoracic location is found in but four cases, or 20 per cent. The bilobed type of thymus predominates in this group with a total of fifteen cases, or 75 per cent. The trilobed type is next in order with three cases, or 15 per cent. The conglomerate is represented by but two cases, or 10 per cent., and there are no unilobed thymus glands present in this group.

These results in regard to lobation agree, in the main, with the findings of most other observers in that the bilobed type is generally described as being the most prevalent.

The thymus is overlapped by the right lung in all members of this group. It is overlapped by the left lung in sixteen, or 80 per cent. of the cases..



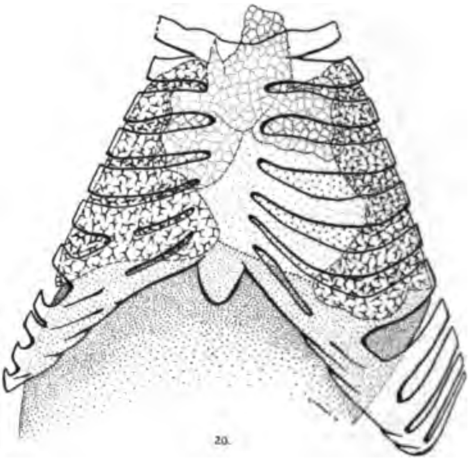


Fig. 19.—A graphic reconstruction of No. 39 (485 mm. long) which is also shown in Figure 2. The overlapping of the thymus by the lung, extent of cervical portion of the thymus, and relation of thymus to sternum and ribs are shown in this and the following graphic reconstructions.

Fig. 20.—Graphic reconstruction of No. 40 (501 mm. long) which is also shown in Figure 3.

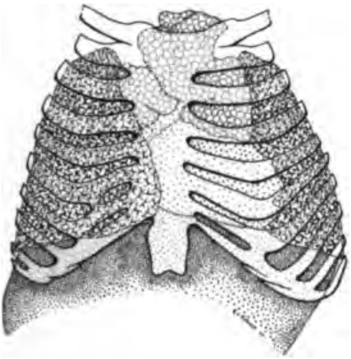
The right portion of the thymus extends on the right ventricle of the heart in thirteen cases, or 65 per cent. of this group. The entire series shows but 16.1 per cent. and the nonbreathing group shows not a single case.

The left portion of the thymus extends on the right ventricle in sixteen cases of this group, or 80 per cent. The nonbreathing group shows but 4.4 per cent.

The broad type of thymus occurs in but five cases, or 25 per cent. in this group, and the elongate thymus in fifteen cases, or 75 per cent.

III. DISCUSSION

A. *The Fetal Thymus and its Transformation in the Neonatal Period.*—From the observations recorded above it is seen that the thymus in the latter part of fetal life is quite constant in its form, and in its relation to other organs and structures in the thoracic and cervical regions. Its location may be either thoracic or cervicothoracic with the latter location the more frequent (i.e., in about four out of five cases). The organ is distinctly broad in outline, extending laterally as far as the anterior axillary lines in most cases. The number of lobes in the majority of cases is two—this type of lobation being substantially the same as is found in postfetal life. The fetal thymus is practically never overlapped by either lung, thus leaving its anterior surface directly in contact with the posterior surface of the anterior chest wall.



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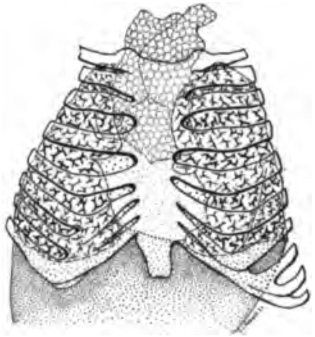

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Fig. 21.—Graphic reconstruction of No. 31 (402 mm. long) which is also shown in Figure 4. The extension of the thymus over the ventricle on the left side is clearly shown. The right lung has almost reached the midline, but the anterior margin of the left lung is still a great distance from it.

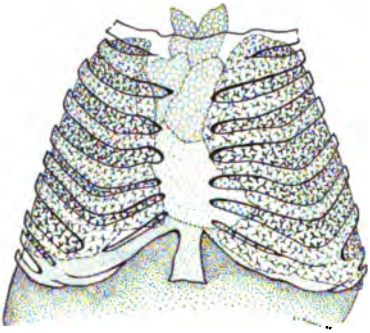
Fig. 22.—Graphic reconstruction of No. 34 (401 mm. long) which is also shown in Figure 6. The overlapping of the thymus by both lungs, and the extent of the thymus inferiorly on the right ventricle is well shown.

Inferiorly, the organ does not extend, on either side, on the surface of the right ventricle of the heart. The probable explanation of the broad type of thymus in late fetal life lies in the constant increase in the relative weight of this organ during the last few months before birth. This fact is clearly brought out by the collected data on the weight of the fetal thymus recorded in this laboratory.

The distinctly broad type of thymus described above as being of the fetal type is also found to be typical of full term stillborn children. This is shown in Figure 31 (No. 60 of the series) of the thymus of a full term stillborn child. The lungs in this case did not extend on the anterior surface of the thymus nor did this organ show any evidence of molding.

The thymus in the infant in which respiration has been partially or wholly established, like that of the late fetus, is usually cervicothoracic in location and is also, in most of the cases, composed of two lobes. But it is elongate in form and bears the impress of the organs with which it is in contact. The right lung extends on its anterior surface in every case and the left lung extends over its anterior surface in four out of five cases. The thymus overlaps the right ventricle of the heart on the right side in more than 50 per cent. of the cases, and on the left side in over three-fourths of these individuals.

The transition from the broad or fetal type to the elongate and molded type of thymus found in the individuals who have breathed is accomplished during the time in which respiration is completely established. The expansion of the lungs changes the position and relations of the thoracic contents, and along with the other organs and viscera of the thorax the thymus is markedly affected. It is compressed both laterally and anteroposteriorly, with the resultant elongation and molding, and extension over the right ventricle.



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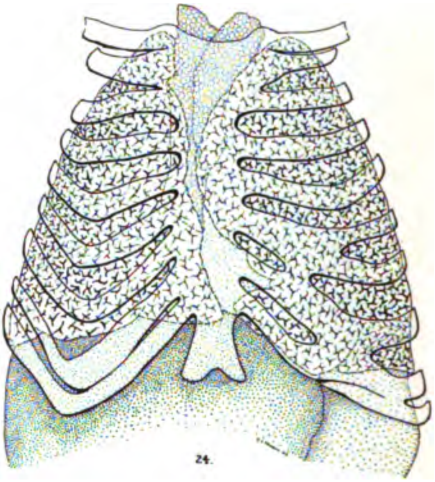

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Fig. 23.—Graphic reconstruction of No. 32 (412 mm. long). The anterior dissection is shown in Figure 7.

Fig. 24.—Graphic reconstruction of No. 41 (510 mm. long) also shown in Figure 8. The extent of thymus overlapped by the lungs is indicated by the broken line. The cervical portion of the thymus, and the relation of the thymus to the ribs and sternum are clearly shown in this drawing. The longitudinal axis of the heart, in this case, is much more nearly vertical than in any of the other individuals in the series. It will also be noted that the anterior-inferior angles of both lungs extend slightly below the angle of the costal arch. The outline of the thoracic cage, on comparison with the cases which have breathed less, shows that it has become more narrow and ovoid in shape.

The thymus glands of infants who have breathed a very short time show but little change in form or relations from the broad or fetal type. This is well shown in Figure 33 (No. 65); (congenital cystic kidneys). This infant had lived half an hour, and in that time the thymus was but very slightly molded. The right lung overlapped the thymus slightly as did also the left lung. The thymus was flattened on the left side but not at all on the right. The right lobe was very large and extended posteriorly to a marked extent. On making the floating test, it was found that only a small part of the right lung floated, whereas the entire left lung did so. I am inclined to believe that the very large right lobe of the thymus compressed the bronchus, thus interfering with the expansion of the right lung.

The molding of the thymus seems to be quite closely related with time in the neonatal period. This is well shown in Figures 31 to 36, inclusive. The thymus of an infant which had lived four hours (cerebral hemorrhage) is reproduced in Figure 32 (No. 64). In this case the thymus was overlapped by both lungs and was molded by them. The organ also extended on the right ventricle on the right side. Figure 34 is a drawing of series number 61, a premature (whose abortion was induced by overactivity on the part of the mother) which had lived twelve hours. The lungs overlapped the thymus on both sides, distinctly molding the organ so that it presents lateral depressions. On the left side the thymus extended slightly on the right ventricle. It resembles closely number 31 of the series, as may be seen on comparing it with Figures 15 and 26. The thymus of an infant which had breathed twenty-six hours (diabetic mother; cesarian section) is shown in Figure 35. It is number 62 of the series. In this case the lungs overlapped the thymus on both sides, flattening and making definite impressions on them. The thymus is elongated and extended on the right ventricle on the left side. This specimen is very similar to that of number 29, as may be seen on comparison with Figures 16 and 25. The thymus of a 14 months old child was found to be of the elongated type, very thin, and convexly molded by the lungs which completely covered the organ. It corresponds to those usually described for young children and is similar to the figures by Spalteholz[10] of a 12 year old boy.

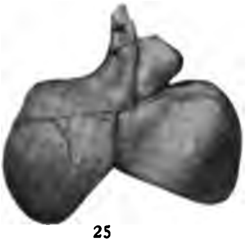
It may, therefore, be said, in general, that the thymus glands observed at necropsy, taken as a group, indicate that the molding and changes in relations of the organ agree with those found in my cadaver series, and that these changes take place very early in life—in fact, during the neonatal period.

Several thymus glands which were removed from individuals who had breathed were drawn to a standard size; these are shown as Figures

25 to 30, inclusive. All in this group are from the cases in which anterior dissections were drawn, except Figures 27 and 29.

This series of drawings shows various degrees of molding of the thymus which correspond with the extent of expansion and consequent compression by the lungs. The transition in form from the broad fetal or stillborn type to the markedly molded and elongated type found in the individuals who have breathed, is readily seen in this group. Most of these thymus glands show a grooving at the level of the sternal notch, thus indicating that the pressure at this point must have been very great.

B. *The Relation of the Thymus to the Anterior Skeletal Wall.*—The relation of the thymus to the anterior skeletal wall in the late fetal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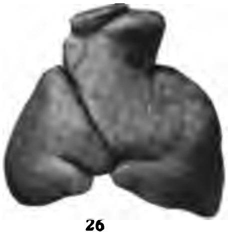
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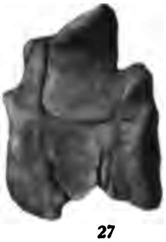
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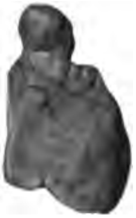
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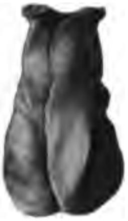
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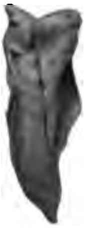
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Figs. 25 to 30 represent a group of thymus glands drawn to standard size illustrating the effect of the establishment of respiration on the form of the thymus.

Fig. 25.—Thymus from Case 39, also shown in situ in Figure 13. This specimen shows a slight molding by the overlapping lungs. Crown-heel length of this specimen 485 mm.

Fig. 26.—Thymus from Case 31 (402 mm. long) shown in situ in Figure 15. The compression by the lungs is here shown by the lateral molding and the anterior depression underlying the sternal notch.

Fig. 27.—Thymus from a full term liveborn infant. Marked molding due to compression by the lungs and a depression at the level of the upper border of the manubrium sterni is well shown.

Fig. 28.—Thymus from Case 29 (374 mm. long) shown in situ in Figure 5. The flattened sides and depression by the upper border of the manubrium sterni are well shown.

Fig. 29.—Thymus of a liveborn infant showing very marked lateral compression; this figure also shows the groove made by the upper border of the manubrium sterni.

Fig. 30.—Thymus from Case 41 (510 mm. long) shown in situ in Figure 18. The marked impression on the left and molding on the right side are well shown. A conception of the great sagittal extent of the organ may be obtained from this picture.

stages and in the new-born may be seen in Figures 19 to 24, inclusive. These are graphic reconstructions of Nos. 39, 40, 31, 34 and 41 of my series. These specimens are also shown in Figures 13 to 18, inclusive.

The degree of expansion of the lungs influences the extent of the thymus lateral to the borders of the sternum and also the extent of the thymus inferiorly. In the late fetus and in the stillborn the thymus extends as far laterally as the anterior axillary line. In cases of slight breathing, it was noted that it was the right lung which had made the greatest advance toward the median line, and that the thymus on this side was less extensive than on the left. The inferior limits of the thymus in the stillborn was, in most cases, at the upper border of the fourth costal cartilage with but a few as low as the upper border of the fifth costal cartilage. In the individuals who had breathed, the lateral extent of the thymus was slight, and occasionally not at all on one side. The inferior limit of the thymus in these cases was, as a rule, somewhat lower. A few were at the level of the upper border of the fourth costal cartilage, but those whose lungs were well expanded extended as far inferiorly as the upper border of the sixth costal cartilage.

In general, the outline of the thymus on the anterior chest wall is described in the literature as a triangular area with the base extending horizontally from one sternoclavicular joint to the other. The sides of the triangle extend inferiomedially from these joints to the level of the second, third or fourth rib—the latter limit varying with different authors. It is held that a thymus lying within the above limits is of normal size, and that if the thymus extends lateral to the sides of the triangle it is probably enlarged. This enlarged or hypertrophied thymus is then suspected of exerting pressure on the structures adjacent to it.

The findings here presented indicate that in the neonatal period, the degree of expansion of the lungs is a more potent factor in determining the lateral extent of the thymus than is the actual size of this organ. In this connection it may be pointed out that during the period of the new-born at least, a thymus lying within the usually described normal area may exert marked pressure on the structures posterior to it. This is the condition which was present in No. 41 of my series of cases. Figure 24 is a drawing of the graphic reconstruction of this case; Figure 18 is from the anterior dissection, and Figure 30 is of the thymus after removal. (See also Figure 45 which shows another case in which the greater part of the thymus has been removed.) I believe as Warthin[7] points out, that the anteroposterior extent of the organ as well as its transverse extent is an important point in determining whether or not a thymus is enlarged.

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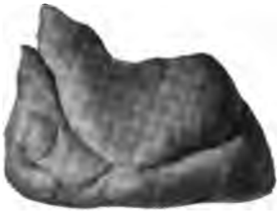
[7] Warthin, A. S.: Pathology of Thymic Hyperplasia and Status Lymphaticus, Arch. Pediat. **26**:597, 1919.

C. *The Posterior Relations of the Thymus.*—The posterior relations of the thymus are in a measure determined by its craniocaudal diameter. A cervicothoracic thymus may extend far into the neck and meet the inferior border of the thyroid, as is the case in Nos. 34 and 40 of my series. In these cases the thymus, after coming in contact with the inferior border of the thyroid, turned anteriorly and laterally. On the other hand, the thymus may extend inferiorly to such an extent that it will lie on the right ventricle.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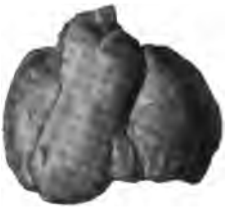
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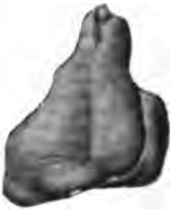
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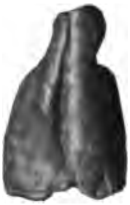
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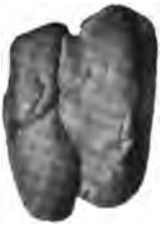
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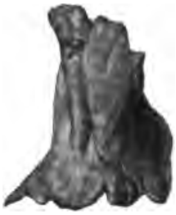
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Figs. 31 to 45 represent a series of thymus glands secured at necropsy and hardened by immersion in chrome-formol. The form of the specimens was preserved by mounting them on pads of cotton.

Fig. 31.—No. 60 (315 mm. long) full term stillborn.

Fig. 32.—No. 64, full term infant which had lived four hours.

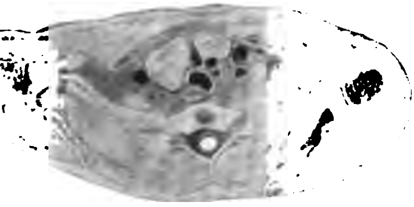
Fig. 33.—No. 59 (370 mm. long) premature infant.

Fig. 34.—No. 61 (305 mm. long) premature which lived twelve hours.

Fig. 35.—No. 62 (450 mm. long) new-born infant which had lived twenty-six hours.

Fig. 36.—No. 63. Thymus of a 14 months old girl. This thymus was markedly molded and compressed. Its anterior-posterior diameter was but 4 mm.

The thymus in late fetal life and in the new-born is related posteriorly to the pericardium over the base of the heart and great vessels. On the left it may extend, in exceptional instances, as in one of this series, to the left vagus nerve. On the right it is generally found to be applied closely to the superior vena cava. The left innominate vein, and, occasionally, the superior vena cava, is embedded in the posterior aspect of the thymus. In a few cases it was found that these vessels actually ran through the substance of the gland. The innominate artery is closely applied to the trachea and crosses it diagonally, and the left innominate vein passes across the artery at the level of the upper border of the sternum. An increase in the anteriorposterior extent of the thymus in this region would, due to the rigidity of the superior thoracic aperture, compress the above named structures. In several of my cases this had evidently occurred. In these specimens the innominate artery was so greatly compressed against the trachea that it left a definite furrow marking its course across this tube thus



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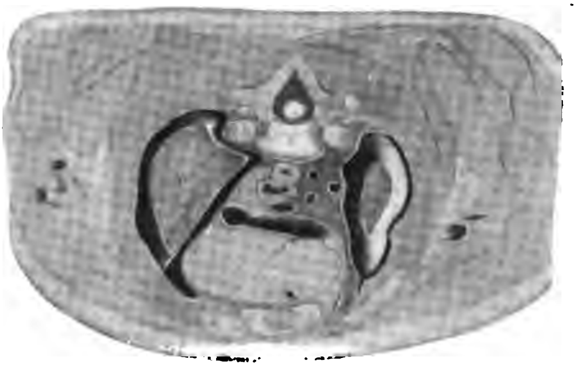

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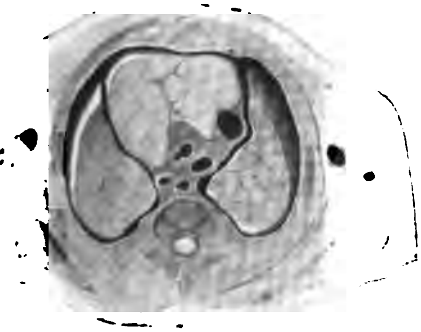
Fig. 37.—Cross section of No. 51 (380 mm.) through the cervical region just above the sternal notch; the thymus is bilobed.

Fig. 38.—Cross section of the thorax of a full term fetus 510 mm. long (stillborn), below the sternal notch and above the aortic arch, showing the broad type of thymus. It will be noted that the innominate vein passes through the thymic substance to join its fellow, and that the thymic substance extends posteriorly as far as the posterior wall of the esophagus.



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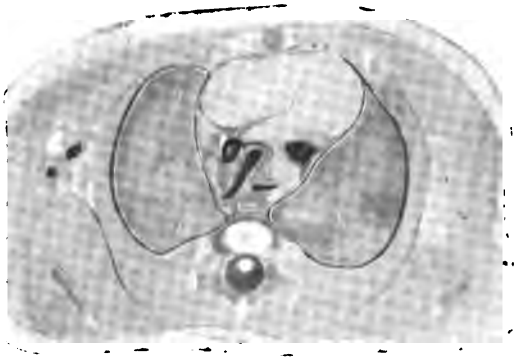

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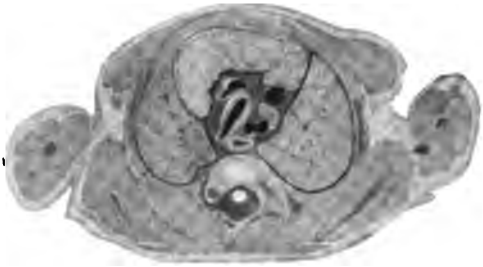
Fig. 39.—Cross section of the thorax of a new-born infant 410 mm. long. This section shows a broad thymus with a rather extensive anteriorposterior diameter.

Fig. 40.—Cross section of the thorax of a stillborn full term fetus (480 mm.). This shows the characteristic broad type of thymus found in the late fetus and stillborn. This section is at the level of the aortic arch and shows a very marked posterior prolongation of the thymus. The convex sides of the thymus, characteristic in the stillborn, is well illustrated here. An evident constriction of the trachea due to partial surrounding by thymic substance is clearly shown.

markedly reducing the lumen. In one case the esophagus was in turn compressed by the trachea so that its right border was reduced to knife-edge while its left border was rounded. In another case, the esophagus had a marked dilatation on the right side just superior to the constriction. In still another case the thymus posteriorly partially enveloped the arch of the aorta so that the transverse diameter of this vessel was only half its anteriorposterior diameter (Fig. 45).

The thymus may not only compress the structures that lie posterior to it, but portions of it may project posteriorly and thus interfere with the structures there situated. An example of this is shown in Figures 43 and 44, which were drawn from series No. 27. This infant, according to the criteria used, had not breathed. The superior portion of the thymus extended posteriorly between the innominate artery and the left common carotid until it pressed against and constricted the trachea. The thymus must have compressed the left innominate vein a little lower so that the artery, in turn, was flattened against the trachea with the consequent constriction of the latter structure. The esophagus in this region in cross-section was somewhat triangular in outline with the sharp apex lying under cover of the trachea. Figure 44 shows the deep groove in the anterior wall of the trachea. This groove was situated just above the level of the sternal notch which thus emphasizes the fact that in the late fetus and in the stillborn the tracheal bifurcation is much nearer the sternal notch than in later life.



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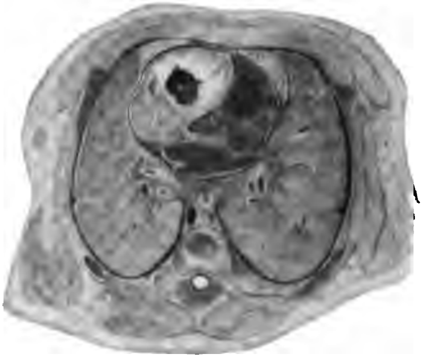

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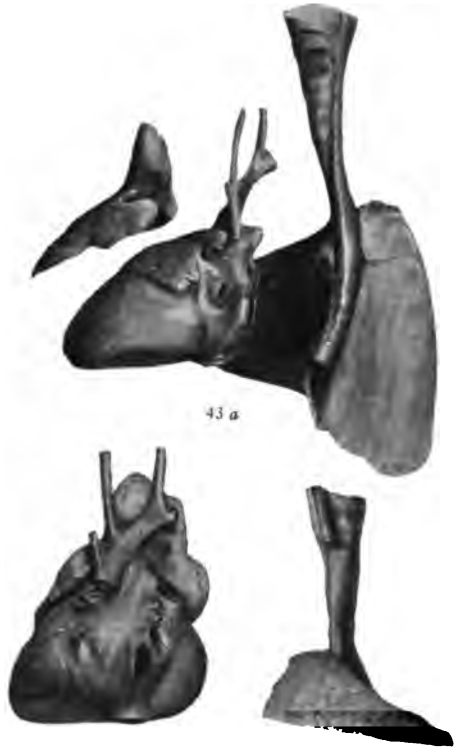
Fig. 41.—Cross section of the thorax of an eight month stillborn fetus (No. 54, 410 mm.) through the level of the aortic arch. This figure shows an isolated portion of the thymus situated between the superior vena cava and the beginning of the tracheal bifurcation. At a higher level this small portion was continuous with the main mass of thymus.

Fig. 42.—Cross section through the atria and the right ventricle of the heart of a new-born infant. The thymus in this case passes over the right atrium and extends on the right ventricle. The flattened left lateral surface, the overlapping by the right lung, and the extent of the thymus on the right ventricle would indicate that this individual had breathed.

The cross sections, several of which are here reproduced, are also instructive from the point of view of posterior relations of the thymus.

A section through the cervical region just above the sternal notch is shown in Figure 37. The thymus in this specimen was bilobed and extended posteriorly on the left as far as the anterior surface of the esophagus. It was also slightly in contact with the left lateral surface of the trachea.



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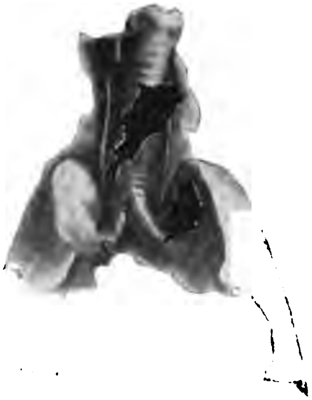
43 c

Fig. 43.—Drawings of Case 27 (premature, 337 mm. long) showing compression of structures posterior to the thymus. (*a*) The molded thymus, compressed great vessels, trachea and esophagus are shown in their relative positions. The thymus shows the grove for the left innominate vein and a posterior-superior knoblike process which projected between the innominate artery and left common carotid and against the trachea which it compressed. The innominate artery is seen to be flattened by the thymus—and in turn compressed the trachea. (*b*) Posterior view of thymus, heart and arteries. (*c*) Lateral view of the compressed trachea showing the markedly flattened right border of the esophagus.

A section through a lower level, i.e., through the manubrium sterni and above the aortic arch of a full term fetus is shown in Figure 38. It shows a broad thymus through which the left innominate vein passed as it joined its fellow forming the superior vena cava. It seems logical to assume from this relation that marked congestion or compression of this thymus would lead to a cyanotic condition of the head, neck and upper extremities. The greater posterior extent of the thymus in this case is on the left side and a tongue-like process extends as far backward as the posterior wall of the esophagus. It is also in contact with the right side of the trachea and has evidently compressed the innominate artery and the trachea to a slight degree.

Figure 39 is of a section through the level of the tracheal bifurcation of a stillborn child. The thymus here is of the broad type with a marked anteriorposterior diameter. On the left side, the thymus is seen to extend even posterior to the trachea though it is not in direct contact with it. On the right side, the anterior surface of the superior vena cava is in direct contact with the thymus and is partially enveloped by it.



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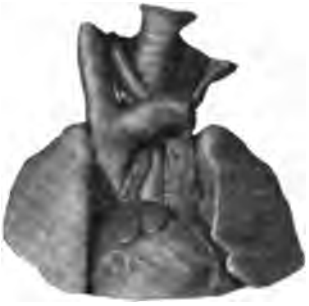

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Fig. 44.—No. 27 (premature 337 mm. long), anterior view of the compressed trachea showing the diagonal course of the innominate artery, as is indicated by the furrow the artery has made on the trachea.

Fig. 45.—Drawing of Case 29 (premature 374 mm. long). The greater part of the thymus has been removed and only enough left so as to show its extent posteriorly. The thymus encloses the aortic arch. The oblique course of the innominate artery as well as its impression on the anterior surface of the trachea is shown.

A section at a lower level—through the arch of the aorta of a stillborn child is shown in Figure 40. We have here a very broad thymus which in this case extends posteriorly to a very great degree. It is seen projecting between the arch of the aorta and the superior vena cava and continues posteriorly as far as the anterior surface of the esophagus. This thymus bears a medial indentation into which fitted the right third of the tracheal bifurcation.

Figure 41 (stillborn child) is also a cross section through the tracheal bifurcation but at a lower level than the preceding one. It has the broad type of thymus with the lungs not extending over the anterior aspect of the former. This thymus is noteworthy, due to the posterior projection which is here shown as an isolated mass. This mass was continuous with the main part of the thymus at a higher level. At this level it is situated between the superior vena cava and the tracheal bifurcation.

A transection through a much lower level (Figure 42, through the heart) shows the thymus extending on the right ventricle on the left side and the overlapping of the right atrium on the right side. The left lung does not extend on the anterior surface of the thymus but the right lung does so slightly, thus indicating that this individual had breathed at least to a limited extent.

D. *Form and Topography of the Thymus in Infancy and Childhood as Described in the Literature.*—The descriptions and figures of the thymus which are presented in the various texts, atlases and clinical publications give little indication of the changes in form and relations which the organ undergoes in the neonatal period. This is true despite the fact that the literature contains many figures of "new-born" thymus glands which vary widely in size, form and relations.

Applying the same criteria to descriptions and figures of the thymus glands in the literature as was used for the material presented here, it is possible to discern the same two general types, i.e., broad and elongate. At least three-fourths of the descriptions and illustrations of the thymus in the new-born conform to the type designated as "broad."[8]

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[8] Cooper, A.: The Anatomy of the Thymus Gland, American Edition, Philadelphia, 1845.

Luschka, H.: Die Anatomie des Menschen, 1863, Tübingen **2**:324, et seq., Figure 26.

Mettenheimer, H.: Topographische Anatomie der Brust des neugeboreneu Kindes, Morphol. Arbeit. **3**:302 et seq., 1894.

Gegenbaur, C.: Lehrbuch der Anatomie des Menschen, Ed. 6, 1896, **2**:123, Figure 463.

Chievitz, J. H.: Topographical Anatomy of a Full-Term Human Fetus in Situ, Copenhagen, 1899, Figure 7.

Zuckerkandl, E.: Atlas der Topographischen Anatomie des Menschen, 1914, p. 244, Figure 288.

Sobotta, J.: In Bardeleben, Handbuch der Anatomie des Menschen, pp. 116, 122, 129; Figures 3, 9, 13; 1914.

Fetterolf, G., and Gittings, J. C.: Some Anatomic Features of the Child's Thorax, Am. J. Dis. Child. **1**:6 (Jan.) 1911.

Cunningham: Textbook of Anatomy, Ed. 4, 1913, pl. 1349, Figure; 1059.

Quain-Schaeffer: Elements of Human Anatomy, Ed. 11, 1914, **2**:2, p. 325.

Rauber-Kopsch: Lehrbuch der Anatomie, 1914, **4**: p. 236, Figure 289.

Coplin, W. M. L.: loc. cit.

Hammar, J. A.: Gewisse Fälle von Thymus Asthma im Lichte der Thymustopographie, Ztschr. f. Kinderh. **13**:226 et seq., 1915; Figures 4, 5, 6.

Sjollander, A., and Strandberg, A.: Om nerverna till thymus, Upsala Läkareförenings Forhandlingar **20**:244, 1915.

Gray-Lewis: Anatomy of the Human Body, 1920, p. 1273, Figure 1178.

I found but three instances in the literature in which the thymus of the new-born is described as elongate, and only three illustrations which show this form of thymus at birth.[9] The descriptions and illustrations of thymus glands in individuals one month and older are all of the elongate type.[10] All of the broad type thymus glands in the literature have corresponding cases in the present series. Since they are of this type, and are not at all overlapped or molded by the lungs, and have counterparts that have not breathed, I conclude that they are from stillborn individuals.

The above mentioned illustrations and descriptions from the literature show clearly the use of both broad and elongate types in descriptions of the thymus in the "new-born." In some cases terms such as "fetus at term," "full term fetus," [11] etc., are used. In the latter, the thymus glands illustrated or described are evidently from liveborn individuals.

These terms are confusing, and it seems that the terms "stillborn" and "liveborn" would be more appropriate in describing organs in the new-born since it is evidently to the living that the information will be applied.

I have been able to find but three references in the literature which indicate that the establishment of respiration has any possible connection with the form and relations of the thymus. Sappey [12] states that the thymus in the infant which has not breathed is of large size, thus suggesting the broad type. Hammar [13] in discussing the thymus in the new-born describes it as a distinctly wide organ whose lateral sur-

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9. Huntington, G. S.: Topographic Anatomy of the Thorax in the Fetus at Term. Report New York Lying-In Society, 1897, New York.

Poirier and Charpy: Traite d'anatomie humaine, Ed. 2, 1911, 4:568, Figure 304.

Testut and Jacob: Traite d'anatomie topographique, Ed. 2, 1909, 1:839, 840, Figures 592, 593.

Corning, H. K.: Lehrbuch der topographische Anatomie, Ed. 3, 1911, p. 304, Figure 237.

Bardeleben, K.: Atlas der topographische Anatomie des Menschen, 1906, p. 63, Figure 118.

Morris-Jackson: Textbook of Human Anatomy, Ed. 5, 1914, p. 1320, Figure 1074.

10. Joessel, J.: Lehrbuch der Topographische Chirurgischen Anatomie, Bonn. Ed. 2, 1899, p. 74, Figure 16.

Piersol, G. A.: Anatomy of the human body, Philadelphia, 1908, p. 1273, Figure 1178.

Olivier, M. E.: Anatomie topographique et chirurgie du thymus, Thèse Par., 1911.

Sobotta, J.: In Bardeleben. loc. cit.

Spalteholz, W.: Handatlas der Anatomie des Menschen, Ed. 3, 1920.

11. Huntington, G. S.: loc. cit.

12. Sappey: Traite d'anatomie descriptive, Ed. 4, Paris, 1889, T. 4, p. 472, Figure 862.

13. Hammar, J. A.: 1915, loc. cit.

faces are markedly convex, bulging into the pleural cavities. He states that in the course of postfetal life the form of the organ changes into a less wide and more lengthy one, but that he is unable to say at which time the relations of the thymus in the new-born are replaced by those prevailing in the older individuals. However, he makes the suggestion that this change may take place in some definite relation to breathing. Hammar's illustrations of a dissection of the thorax of the new-born child clearly show the decidedly broad type of thymus; and the anterior borders of the lungs are sharp and do not overlap the anterior aspect of the thymus. Since the margins of the lungs in Hammar's figures are so sharp, and since there is no molding of the thymus by the lungs, it is most probable that these individuals must have been stillborn. This conclusion is further strengthened by the examination of Hammar's cross section figures of the new-born child. In these the thymus is extremely broad, and its lateral surfaces bulge into the medial surfaces of the lungs which do not overlap the anterior surface of the thymus in the slightest degree. His picture of the thymus shows it to be of the distinctly broad type. Apparently, the material used by Hammar was stillborn.

Since the completion of the work on which this paper is based there has come to hand a recent issue of the Anatomische Hefte containing an article by Graper.[14] In his discussion of the thymus he draws some conclusions which are similar, in part, to some of the results obtained by me. Graper states that the form of the thymus is altered during the first few breaths. It is compressed laterally by the expanding lungs and as a result its sagittal diameter is increased. He finds that after compression the thymus is triangular in cross section with the base of the triangle posterior, and that the elevation of the anterior chest wall during the establishment of respiration creates a space into which the thymus accommodates itself. His conclusions are based on a study of over fifty preserved cadavers but are not checked by necropsy findings.

The descriptions and figures in the literature of thymus glands of children later than the neonatal period [10] (especially in early childhood) are all of the elongate type and show marked molding by the lungs. Sobotta, in Bardeleben,[10] has a picture of the thymus of a 2 year old child. Even though it is not in situ, it is seen to be elongate and molded. He also presents an anterior dissection of a 14 year old girl. The thymus is markedly elongate and molded. Piersol [10] illustrates a cross section of the thorax of a child about one year old. The thymus is overlapped by the right lung and thus molded. This is also an elongate thymus; however, I have seen corresponding thymus glands in much younger individuals. Olivier[10] presents a drawing of a dissection of a one month old infant's thorax. He states that it shows the normal type of thymus. It is a bilobed organ whose lobes are widely separated and relatively very small. It is similar to thymus glands which I find in much older children. Since Olivier states that only two of his dissections were of infants, it seems probable that he had in this case the thymus of an infant in which a marked involution of the thymus had occurred.

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[14] Graper, L.: Die anatomische Veränderung kurz nach der Geburt. Anatomische Hefte 59:45, 1920.

4. RÉSUMÉ

1. The lobation of the thymus is determined early in fetal life and the establishment of respiration obviously has no effect on it.

2. The thymus in the late fetus and in the new-born is predominantly of the cervicothoracic type, i.e., its position is intermediate between the cervical location in the embryo and the thoracic location of the older infant, child and adolescent.

3. The thymus in the late fetus and stillborn child has a typical form and quite constant relations. Its lateral surfaces are convex and bulge against the medial surfaces of the lungs. The lungs very rarely extend at all on its anterior surface, and the thymus very rarely extends at all on the anterior surface of the right ventricle of the heart.

4. The thymus in liveborn infants has typical form and relations which are similar to those found in young children. It is elongated and molded so that its anterior, lateral and posterior surfaces bear the impress of all the organs with which it is in contact. Its lateral surfaces usually show marked convexities which are occupied by the lungs which pass over the anterior surface of this organ. Unlike the fetal thymus, it usually extends more inferiorly passing over the right ventricle.

5. The change from the broad or fetal type of thymus to the elongated and molded type found in the liveborn and in the young infant bears a direct relation to the establishment of respiration, and is dependent on the expansion of the lungs. The organ is compressed from side to side by the medial surfaces of the expanding lungs. It is compressed anteroposteriorly by the anterior borders of the lungs which become much thickened early in the establishment of respiration as they gradually overlap the thymus.

6. In some cases the thymic substance may extend posteriorly at birth to such an extent that the structures situated there are compressed by it. This may be due either to an unusually large thymus or to a very narrow superior thoracic aperture which will not allow the thymus to protrude into the cervical region as it is compressed by the expanding lungs.

7. The descriptions and illustrations in the literature of the thymus in the new-born child show great confusion. They include both the fetal (broad) and infantile (narrow or elongate) types and the distinction between the two has evidently passed unrecognized. The type of thymus which is the more frequently described as characteristic of the new-born and the infant is the one which the preceding data indicate is usual for the fetus and stillborn as contrasted with the living infant.

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FIVE HUNDRED AND THIRTY-FIVE NORTH DEARBORN STREET
CHICAGO

hypophysis. An examination of the principal observations upon which this idea rests may serve to place the subject in its proper setting.

In reviewing the literature on the theories of hibernation the writer ('16) called attention to the large number of authors who considered hibernation among the higher forms, at least, as merely an extreme form of ordinary daily sleep as seen in man and mammals. Hibernation, therefore, naturally suggested itself as being a favorable condition for investigating the factors involved in the production of sleep. Attention was also called to the views of Salmon ('05, '10) who argued that by virtue of some vasomotor or toxic power on the nervous system, the hypophysis is a center for the production of normal sleep . He discusses his theories again in 1916.

From the two preceding assumptions—(1) ordinary sleep and hibernation are merely degrees of the same phenomenon and (2) the hypophysis is a chief center in the production of sleep—Gemelli ('06) was led to a histological examination of the hypophysis of twenty-two adult European marmots (Marmota marmota). Some of these were sacrificed while hibernating and others during the active state in the spring and summer. He found no changes in pars nervosa (processus infundibuli) nor in pars intermedia (juxta-neuralis); but in pars anterior (distalis) a great reduction in the chromophilic cells during dormancy was observed—suggesting a stage of lessened activity. He, therefore, concluded that Salmon's view could not be correct because such a view involved a stage of hypersecretion on the part of the hypophysis during winter sleep. He further noted many mitotic figures in the spring after waking up. This would indicate that the time of greatest activity on the part of this organ was not during dormancy but after the animal becomes active.

The hypophyses of seven American marmots (Marmota monax), which like the European species have several months of profound dormancy (Howell '15), were examined microscopically by Cushing and Goetsch ('13, '15). Here particularly the hypophysis of hibernating animals was compared with that of the active animal of early spring. They interpret their findings as confirming in general the statements of Gemelli on the decrease in size of the whole organ and the loss of specific staining reaction of the cells of pars anterior during winter-sleep. In their summary they state: "The gland not only diminishes in size, but the cells of the pars anterior in some animals at least completely lose their characteristic staining reaction to acid and basic dyes. At the end of the dormant period the gland swells, and as the cells enlarge they again acquire their differential affinity for acid, basic, and neutral stains and at the same time karyokinetic figures may appear" ('15 p. 46). They suggest that hibernation may be ascribed to a period of physiological inactivity possibly of the entire ductless gland series, but certainly more especially of the hypophysis. They cite clinical and experimental cases showing a distinct tendency to somnolence, storage of fat, subnormal temperature, slow pulse and respiration, lowered blood pressure and retardation of sexual development in hypopituitarism. One must agree that these symptoms suggest a tendency towards the conditions prevailing during winter-sleep of animals and that the tendency to associate certain forms of morbid somnolence with functional disturbances of the hypophysis (Dana '16) is well founded.

A far more extensive study of the ductless glands in relation to the onset of hibernation was carried out by Mann ('16) on the thirteen-lined ground squirrel (Citellus tridecemlineatus). From this study there was no suggestion of a distinct relation of the ductless glands to the production of lethargy. With reference to the hypophysis he found in some cases during dormancy a loss of the differential staining qualities of the granular cells of the pars anterior, some decrease in the size of the cells and an irregularity in their grouping. But these changes were inconstant and in several hibernating animals the hypophyses could not be distinguished from those of active ones.

The above summary shows that the results of Gemelli and of Cushing and Goetsch on the marmot as interpreted by them tend to show that there exists a stage of hypofunction on the part of the hypophysis during hibernation. The combined studies upon which this conclusion rests involve a total of twenty-nine animals. It appears, however, that the comparison was made largely between the dormant state and the active state following hibernation. It is clear, as pointed out by Mann ('16, p. 176) that the critical period is that just preceding hibernation. It is the conditions of this period that should be compared with those prevailing during subsequent dormancy. This point is of special importance in animals that are sexually active only during the spring immediately after waking up, because of the probable close interrelation of the gonads and the hypophysis, a relationship which is generally accepted.

That there is some influence of the sex glands on the hypophysis rests largely upon the effects following castration and spaying. Observations on these effects (for review of the literature see especially Livingston '16, Addison '17a) are, however, conflicting. It appears that in the case of the albino rat Hatai ('13b) found it was only the male hypophysis that was markedly affected (enlarged) by gonadectomy. Addison ('17a) showed that this enlargement was accompanied by hypertrophy of the basophilic cells of pars anterior. Others have recorded enlargement of some of the other types of cells in a number of other animals. In the rabbit, Livingston ('16), who submits by far the most accurate data on this species, found no constant effect on the weight of the hypophysis by spaying and castration; while a more recent study on the rabbit by Hayami ('19) corroborates the findings of some of the earlier workers on this species by reporting hypertrophy of the hypophysis as a result of castration and of vasectomy followed by Röntgen rays treatment, the causal factor being the interstitial cells of the testis. Bell ('19, p. 195) also finds evidence of increased secretory activity in the anterior lobe and in pars intermedia after oöphorectomy in the cat, especially in regard to the eosinophilic cells.

The relationship of the gonads and hypophysis, as far as the influence of the latter on the former is concerned, is better established and is evident from the sexual disturbances accompanying disease of the hypophysis found recorded extensively in clinical literature. Extracts of the hypophysis, especially of pars anterior, are reported to stimulate the growth of the sexual glands (Goetsch and Cushing '13, Goetsch '16) although Hoskins ('16) and others (for a review of the literature see Hoskins' paper) fail to corroborate this. Such extracts are also apparently beneficial in some cases of sexual impotence (Stelwagen '16). Other generative structures are also influenced by the extract. This is particularly true of a stimulating effect on the mammary gland (Ott and Scott, Schäfer and Mackenzie, Herring, Gavin, Hammond, Simpson and Hill, Gaines, Houssay and co-workers—literature well reviewed by Hill '16, Houssay '18).

While Cushing and Goetsch did not have the sexual glands from all their animals, they make the assumption that a very marked activation occurs in the reproductive organs when the animals emerge from the dormant state, "and it is tempting to attribute this to the influence of the functionally reactivated pars anterior" ('15, p. 41). In two previous publications the writer ('17, '18) has fully corroborated this surmise by describing the marked enlargement of the testes and ovaries which occurs during the spring awakening in the American marmot. These studies showed a suddenly increased activity both in spermatogenesis and oogenesis and a distinct hypertrophy of the interstitial cells at that time.

So it is obvious that a difference between the hypophysis of the hibernating period and that of the unusually active period immediately following, which is the rutting season, gives no valid evidence regarding the modification of the hypophysis during the dormant state. What occurs during this spring awakening is unusual activity following a long state of rest in most of the physiological processes but especially in those involved in the sexual cycle. It follows, then, that there is needed in the case of the marmot a careful comparison of conditions just preceding hibernation with those of lethargy in order to determine if there are significant structural changes detectable in the dormant animal. This apparently has not been made.

Finally all the data so far submitted are only roughly quantitative. The time has come, as has recently been emphasized by Hammar ('20), when it is necessary to extend anatomical data, particularly on the glands of internal secretion, upon a more accurate quantitative basis, in order to facilitate the making of reliable deductions from pathological and experimental material. Since there are at least three more or less distinct components (Tilney, '13, recognizes at least four) in this organ, each probably of different functional significance (most strikingly brought out recently by Allen '20), these several structures must be investigated. It is conceivable that one part might respond by hypertrophy and yet not be detected by the weight of the whole organ because of compensatory changes in another part, etc.

In view of these conditions and the failure of Mann ('16) to corroborate on another species the reported observations on the marmot, it seemed desirable to extend the inquiry by using more accurate quantitative procedure. There might, of course, be some differences in the way various species respond. It was also expected that histological findings in the hypophysis during the very active period immediately after waking up might give facts of importance regarding the response of the various cellular elements to this condition of hyperactivity, and thus add to our knowledge of the significance of the various types of cells described especially in pars anterior.

It is interesting to note that Saito ('19) has reported that in the horse the weight of the hypophysis varies with the month of the year.

MATERIAL AND METHODS

The material upon which this report is based consists of the hypophyses of thirty-two adult woodchucks from the vicinity of Ithaca, New York. Fifteen of these animals are among those studied for Nissl changes in nerve cells during hibernation (Rasmussen and Myers '16) and are known as Series I in my records. These fifteen and two additional animals (No. 1 and No. 2, Series II) taken together constitute a series of nine males and eight females. One male hypophysis was so damaged in the process of preparation that it was only of cytological value. Of the remaining sixteen perfect organs four (two from males and two from females) were taken before hibernation; four (two from males and two from females), during dormancy; five (three from males and two from females), after waking up but before being fed; three (one from a male and two from females), in the spring while active and after having been fed one, two and three weeks. The smallest male of the non-fed active group that was killed after hibernation, was not used in volumetric calculations, thus leaving in the three principal groups an equal number of each sex and thereby reducing the error due to sex-differences if such differences should exist.

All these animals were killed instantly by transfixing the heart quickly through the chest wall, in most cases without the use of any anaesthetic. Most of the blood was immediately washed out with physiological saline solution at body temperature by perfusion through the aorta. The saline was followed by a saturated aqueous solution of bichloride of mercury to which had been added 10 per cent of formalin. The whole body was thus fixed very quickly while still warm or still cold depending upon whether the animal was active or was lethargic.

Following the removal of the brain, the hypophysis was carefully dissected out and further fixed for 48 hours in a saturated aqueous solution of bichloride of mercury. After washing in running water for 36 hours, the tissue was dehydrated as usual and imbedded in paraffin. The time intervals in the reagents were the same for all specimens so that the shrinkage ought to be very nearly the same in all cases. This point is of importance because the method of fixing *in situ* made it impossible to get the weight of the fresh gland as a check upon volumetric changes produced by the histological technique.

The above material was used for determining the volume of the whole organ and its different parts, the volume of cells and of nuclei, and for a differential count of the basophilic and acidophilic cells of pars anterior. Each hypophysis was cut into serial section 5 μ thick and mounted upon six slides. The plane of section was horizontal, i. e., through the greatest diameter, so as to decrease the number of sections and to present to the best advantage the three principal regions traversed. The first slide was stained with Delafield's hematoxylin and eosin; the second, with methylene blue and eosin; the third, with the aniline blue-orange G-phosphomolybdic acid mixture used in the well known Mallory's aniline blue connective tissue stain; the fourth, with acid fuchsin followed by the aniline blue and orange G mixture as regularly done in Mallory's connective tissue stain; the fifth, with Delafield's hematoxylin and acid fuchsin; and the sixth, with one of the preceding methods depending upon which stain needed checking.

Another series of hypophyses was available from the fifteen animals utilized in the study of the mitochondrial content of nerve cells during hibernation (Rasmussen '19) in the report of which the data concerning the animals are given. They are registered as Series IV and No. 51 and No. 56 of Series III. This material was fixed also *in situ* by injecting Regaud's fixer (one part of commercial formalin neutralized with magnesium carbonate and four parts of a 3% aqueous solution of potassium bichromate) after the blood had been washed out with oxygenated Locke's fluid. The organ was dissected out and further fixed for five days in Regaud's mixture, changing the solution every day, and followed by 3% aqueous solution of potassium bichromate for nine days, changing the solution every day. This preserves the mitochondria well (Cowdry '16). The tissue was imbedded in paraffin with the same precautions exercised with the other material regarding equal duration by all samples in the various reagents including the paraffin bath. Serial sections were cut 5 μ thick until about halfway through the block. The block of tissue and the knife of the microtome were then further cooled by means of a piece of ice held against them. A known number of sections (from 20 to 30) only 2 μ thick were then cut. The rest of the block was cut 5 μ. This gave an uninterrupted series and at the same time enough very thin sections for more detailed study. The 5 μ sections were mounted on about six slides with the point indicated where the thinner sections belonged. Some were stained in hematoxylin and eosin and the remainder for mitochondria in Altmann's anilin fuchsin (20% acid fuchsin in anilin water) and a 1% aqueous solution methyl green (Cowdry '16). Knowing the number of 2 μ sections taken out of the series it was possible to use them for determining the volume of the whole gland and of its various parts since, as will be explained later, it is necessary to use only every tenth section. The 2 μ sections were mounted upon separate slides (three or four sections to a slide) and stained as above for mitochondria after various degrees of dechromation.

The fifteen hypophyses fixed by this second method represent five animals (three males and two females) in each of the first three stages represented by the material first described.

A difference in the fixation necessarily meant that the volumetric data had to be worked out separately for each lot of material. It was found, however, that the figures from each lot were between practically the same limits, dehydration and imbedding having apparently caused sufficient shrinkage to obliterate any differences that might have existed immediately after fixation. For a differential count of the cells of pars anterior only the first described material (formalin-corrosive sublimate fixation) could be used; for mitochondria, only the second (neutral formalin-potassium dichromate fixation). For the rest of the work both lots could be used, the volumetric data being thus based upon thirty whole hypophyses—nine from animals killed before hibernation, between Sept. 4 and Dec. 3, rectal temperature 35°C—38°C; nine from animals sacrificed while dormant, between Feb. 3 and Mar. 18, rectal temperature 7°C to 16°C; nine from animals killed after waking up, between Mar. 16 and April 18, rectal temperature 34°C—37°C; three from animals having been awake several weeks without food and then having been fed one, two and three weeks, killed between April 5 and April 18, rectal temperature 36°C—38°C.

The method of determining the volume of the gland and its various parts as well as the size of cells and nuclei was the paper method of Hammar as used by Jackson ('17). The mathematical basis of this procedure is more fully explained in a later publication (Jackson '19). Suffice it to say that for determining the volume of the whole gland and of the various lobes every tenth section of the series was projected upon standardized paper by means of an Edinger projection apparatus at a magnification of 77 diameters and the various parts outlined, then cut out and weighed. Knowing the weight of one sq. cm. of paper, the surface area of each outlined area is obtained. This was reduced to actual area by dividing by the magnification (77^2) and then multiplied by the thickness ($50\,\mu$) represented by each of the selected sections to give the actual volume. There was left on the organ only an extremely thin fibrous capsule and since the lumen of the residual cavity (intraglandular cleft) and large cyst not containing colloid, or hyaline substance, were discarded when cut out, the weights represent essentially parenchyma and vascular stroma.

In determining the volume of cells and nuclei all the nuclei and vascular stroma in focus at the same time were traced within an area easily outlined by means of a camera lucida and at a magnification of 2100 diameters (Zeiss 2 mm. apochromatic objective, compensating ocular 8). The vascular stroma was cut out and discarded. The remaining paper, represented the essential parenchyma, was weighed. The nuclei were counted, cut out and discarded, and the paper (now representing cytoplasm only) again weighed. The difference between the two weights gives the nuclear area. From these figures and the known weight of a unit area of the paper, the magnification and the number of nuclei (which also represents the number of cells), the average volume of the entire cell and of its nucleus were calculated. In the case of pars anterior this was carried out on four different regions on a section passing through the organ near its greatest diameter. These regions were selected from about the same positions in each case. These are indicated by the four crosses in figure 1. There is sufficient variation in the cells in different parts of the lobe and a fair degree of regularity in the positions where these differences are located to make this procedure necessary. Each of the four areas contained from 61 to 154 nuclei and the four together involved in the neighborhood of 300 nuclei. In pars intermedia only two fields were taken—one from about the middle of each lateral half as viewed in sections passing through the greatest diameter of the whole gland. The cells bordering the residual cavity as well as those next to pars nervosa were not included in the area outlined because these are invariably smaller (fig. 4) than those forming the main bulk of this lobe. In each field in pars intermedia 35 to 85 nuclei were outlined and the two fields together yielded in the neighborhood of 100 nuclei.

The method of cutting out the nuclear areas is of some consequence on account of the tedious task which it involves in an extensive research. Jackson used a sharp scalpel and placed the paper on a wax plate such as is used for reconstruction in the making of anatomical models. The wax plate renders cutting easy but small particles of the wax composition may adhere and if unnoticed produce an appreciable error. The main objection, however, is that it is fatiguing to the hand. While it is no quicker, it is much easier and just as accurate to cut out even the smallest nuclei by means of a fine manicuring scissors with increasing curvature toward the point. One can cut for hours without inconvenience. When a nucleus has been cut out a slit is made from the resulting hole over to the nearest nucleus, etc. When the paper becomes too frail one blade can be inserted into the outlined nucleus and the area excised without communicating with any other hole.

In making the differential count of cells in pars anterior only the granular or so-called chromophilic (acidophilic and basophilic) were enumerated—these being in the minority and the cells usually associated with active secretion. In each animal an entire section near the greatest diameter of the organ was explored systematically by means of a mechanical stage from side to side, stopping for a count as soon as all parts of the previous area had passed out of the field of vision. A section explored in this manner yielded from 206 to 284 fields, with a total count of 8,759 to 13,086 acidophiles and 263 to 3,572 basophiles. To detect any distinct variation in the proportion of the three types of cells it was deemed sufficient to determine the average number of cells of the two types per field, since it had previously been found that there was no marked variation in the size of the cells taken as a whole, from which it follows that the average number of total cells in a unit area (say an entire microscopic field where the magnification, lenses, etc., are kept constant) would be the same in the different stages.

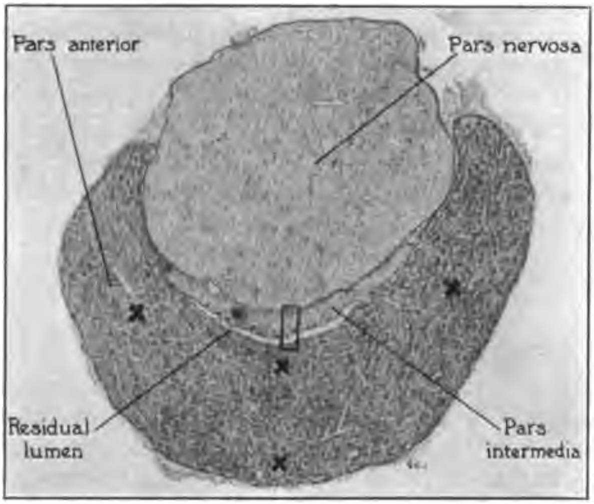

Fig. 1. Horizontal section through the hypophysis of the woodchuck at about the greatest diameter showing the general arrangement of parts. Formalin-corrosive sublimate fixation; methylene blue-eosin stain. X 20.

DESCRIPTION OF THE HYPOPHYSIS OF THE WOODCHUCK

a. General features

The main bulk of the hypophysis of the woodchuck (as already briefly described by Cushing and Goetsch '15) is a flattened disc from 3 to 4.5 mm. in diameter and from 1 to 2 mm. in thickness near the center and thinner towards all edges (dimensions obtained from the fixed material). It lies horizontally in a very shallow sella turcica. The glandular portion forms a distinct crescentic mass half encircling the nervous portion, as shown in figure 1. The infundibular stalk is short and delicate and breaks readily close to the distal enlarged portion. Only in a few cases was much of the infundibulum and adjacent portion of the tuber cinereum retained. From these it appears that all the regions recognized by Tilney ('11, '13) are present. The infundibular stalk is solid through its greatest extent so that it belongs in Vincent's ('12) third class represented in man, monkey, ox, pig, rabbit, etc. It is accompanied by a thin layer of glandular tissue, two to four cells in thickness, continuous below with the main bulk of pars intermedia. The cytoplasm of the cells of this thin layer is much less abundant, the nuclei are slightly smaller and more nearly spherical and stain more deeply than in the cells which form the greater part of pars intermedia. The cells are arranged in anastomosing strands in a stroma almost as vascular as that of pars anterior. The extent to which they surround the infundibular stalk cannot be determined from the material at hand.

The thin layer of cells just described becomes thicker as it spreads out on the under surface of the eminentia saccularis of the tuber cinereum. Thus there is what Tilney terms a pars tuberalis in the juxta-neural glandular tissue. The extent of the pars tuberalis cannot be described here because not enough of the hypothalamus was retained in any case.

The part of the gland primarily investigated was only the enlarged disc-shaped portion consisting of processus infundibuli, which will be designated by the more familiar term pars nervosa; that part of the glandular pars infundibularis that is associated with processus infundibuli, which will be spoken of as pars intermedia; and pars distalis, or the main body of glandular tissue, which will go by the better known name of pars anterior. If additional structures were present they were excluded from the tracings. The point where the pars nervosa rather suddenly narrows down to become the infundibular stalk, a point which is also the upper limit of pars anterior, was taken as the upper boundary line and, therefore, only that portion of the gland below this level is included in the volumetric data. The naked infundibular stalk was always present above this line but pars intermedia usually broke at this point or slightly above except in a few cases where the line of separation was through the floor of the third ventricle. The structures included constitute, however, the better known parts and by far the main bulk of the organ.

b. Pars nervosa

Pars nervosa is solid and pear-shaped, with the infundibular stalk representing the stem. In cross section it is nearly round (fig. 1). A very thin fibrous capsule covers the entire surface. There are no histological features that are either unique or of importance, but they conform to the general description given for other mammals. Fibers constitute the main bulk. It is well supplied with blood vessels. Small masses of homogeneous colloid-like material, somewhat larger than the cells present, are scattered about in all parts of the lobe. They lie free in interstitial spaces.

c. Pars anterior

Pars anterior is crescentic in shape and closes in around the lateral borders of pars intermedia so as to come in contact with pars nervosa (fig. 1). It is also invested with a delicate fibrous capsule. The cell arrangement is of the most common type, namely, irregular anastomosing cords separated by a rich system of sinusoidal capillaries (figs. 1 and 2). Nothing simulating acini was seen strictly within pars anterior.

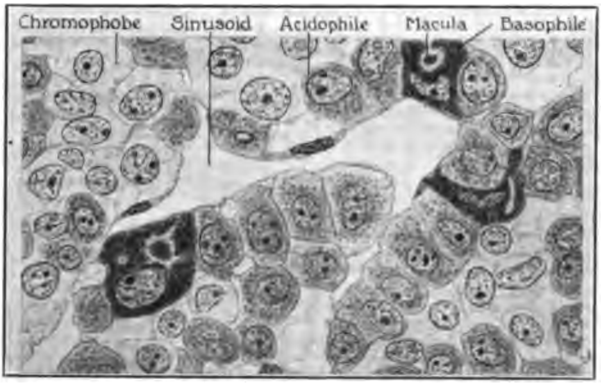

Fig. 2. Small area of pars anterior showing types and arrangement of cells. Formalin-corrosive sublimate fixation; Mallory's acid fuchsin-aniline blue-orange G connective tissue stain. X 1000.

The cells appear to be of three distinct types, usually termed chromophobes but also termed chief cells and reserve cells (lightly staining and devoid of many coarse granules), and acidophilic and basophilic chromophiles (staining intensely due to the presence in the cytoplasm of coarse granules which are either distinctly acidophilic or distinctly basophilic). As shown in figure 2 where the three types are shown in three tones of shading, there is a striking absence of intermediate forms. These three types of cells were found to stand out most clearly tinctorially with Mallory's acid fuchsin--aniline blue—orange G connective tissue stain after formalin-corrosive sublimate fixation. For a study of basophiles, as was also the experience of Addison ('17), omitting the acid fuchsin gives the clearest preparation with maximum contrast. The basophilic cells take the aniline blue and, therefore, stand out in great contrast against the yellow acidophiles and almost colorless chromophobes. However, the acidophiles are best seen when stained with acid fuchsin. As shown by Cooper ('19) it is the same cells that stain intensely yellow with orange G and intensely red with acid fuchsin.

The chromophobes are somewhat more numerous than the chromophiles. They form the body of the cords and, while often seen next to the capillaries, do not show much tendency to border on the blood channels. They vary much in size, a few being among the larger cells encountered while most of the smallest cells are of this type. As has often been noted, the boundaries of the individual cell are difficult to make out with most stains. The mitochondria (fig. 3) are mostly granules ½ μ or less in diameter. Short rods are often seen and occasionally a rod as long as 2½ μ as well as comma-shaped mitochondria are observed. If the cytoplasm is scanty, the mitochondria may be reduced to a single perinuclear layer. The nucleus is of the usual type, either round or somewhat elongated, rather smooth in outline and containing from one to three nuclei and a fairly coarse chromatin network.

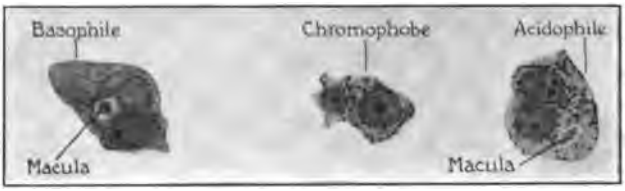

Fig. 3. Cells from pars anterior showing the mitochrondrial content. Neutral formalin-potassium dichromate fixation; acid fuchsin-methyl green stain. X 1000.

The acidophiles are somewhat less numerous than the chromophobes. They are, on the whole, slightly larger and show a decided tendency to occupy the periphery of the cell cords so that they are mostly found directly in contact with the endothelium of the vascular channels (fig. 2). This arrangement has been repeatedly noted in other animals by various investigators. Uniform, round granules fill much of the cytoplasm, especially next to the nucleus. The margin being usually less densely packed with these acidophilic bodies, the limits of the individual cell are fairly distinct. In some of the larger cells there is a lighter colored area resembling a large vacuole in the interior of which is a body possessing the same staining properties and granules as the denser cytoplasm. Addison (17a, b) has discussed this structure under the heading ''Golgi apparatus'' and upon the basis of his work on the albino rat after castration considers it to be a definite cell organ. Gemelli ('07 and earlier publication listed in this reference) has also described large vacuoles and a Golgi reticulum in the chromophilic cells. In the woodchuck material here described this structure has been designated ''macula''—the term tentatively applied by Addison ('17a). This structure is seen in the acidophiles best in the material fixed in neutral formalin-potassium dichromate and stained with acid fuchsin—methyl green, but even then only in a small percentage of the cells; although it is very likely present in a great many more, if not in all, but in a smaller and less conspicuous form. It is probable that with the technique used here it shows up only in the cells where the light zone has been greatly exaggerated by the action of the reagents. One of the largest and most conspicuous maculae observed in the acidophiles is sketched in figure 3.

Mitochondria are present in large numbers (fig. 3). They differ in no way from those already described. It is difficult to be sure of the relative number of mitochondria by the method here used because the large acidophilic granules also take the fuchsin stain and if dechromation is carried to the extent that these larger granules do not stain red, one cannot always be sure of having brought out all the mitochondria present. However, their small size and deep red color make their identity fairly certain even when the cytoplasm is still somewhat red.

The nucleus is slightly eccentric but in structure differs in no particular from that of the chromophobes.

The basophilic cells are least numerous, there being only about one of these to every ten acidophiles. Under usual conditions there is, however, a great variation between individual animals. In one case there may be as few as one basophile to about thirty acidophiles and in another animal as many as one basophile to three acidophiles (table 4). In nearly all cases they are more numerous towards the periphery of the lobe but not at the extreme edge. This peripheral distribution has been seen in other animals (Tilney '11), but denied by Jackson ('17) as a characteristic feature in the albino rat. They occur singly, as a rule, but where numerous may be in clumps so that the majority of the cells in a high power field of the microscope are basophiles. They show some tendency to occupy the regions next to the sinusoidal blood vessels. In outline they are more irregular and as shown in figure 2 may occupy irregular spaces between other cells. The largest cells met with are usually of this type, although there are many medium sized basophilic cells.

The cytoplasm is literally filled with coarse basophilic granules except for a conspicuous light ring or irregular space about a distinct macula, as described in the acidophiles. Practically every cell must contain such a structure, judging from the number of cells in which it is actually present in the section. Naturally a great many cells are so cut that the portion in a particular section does include the macula. This structure varies greatly in size, and to some extent directly with the size of the cell. In the largest cells it may be as large as the nucleus. In the smallest cells it may be smaller than the nucleolus. It is situated most often near the center of the cell. The light area about the macula and the macula itself may be greatly flattened as if by external pressure. While the surrounding vacuole-like region is usually fairly regular in outline, it may be very irregular and branched, as seen in the largest cell in figure 2. In very large cells an additional light area, variable in size, resembling a vacuole, is occasionally seen. The macula shows the same structures and staining reactions as does the dense cytoplasm outside of the light area.

The mitochondria are of the same form as those in the other cells but show a greater tendency to be arranged in rows. They appear less distinct on account of the denser cytoplasm. Probably for this reason they seem somewhat less numerous in proportion to the amount of of cytoplasm than in the other two types of cells.

The nucleus is almost always very eccentric and is very frequently irregular in outline, with a tendency for the concave side to be next to the macula. Its structure does not seem to differ from that of the other nuclei.

As shown in figure 4, the cells of pars anterior which form the anterior wall of the residual lumen are distinctly smaller, more irregular in outline and stain more densely. In some sections these smaller cells form a two layered wall separated from the rest of pars anterior throughout the entire length of the cavity by a plexus of capillaries. These smaller cells are mostly chromophobic in general reaction.

d. Pars intermedia

Pars intermedia, as is clear from figure 1, constitutes a very small part of the hypophysis. Table 1 shows that it may form less than one per cent of the entire organ and is always less than four per cent. It consists of a lamina fairly uniform in thickness usually with a smooth posterior surface, which is closely applied to the thin capsule of pars nervosa. In four out of thirty cases, however, lobules of cells from pars intermedia invaded the neural lobe for a considerable distance. The residual lumen may follow along with this ingrowth. This encroachment of pars intermedia upon pars nervosa has been noted now and then by others. Herring ('08) in his description of the mammalian hypophysis states that this is most frequently met with in the region of the neck of the gland and that islets of epithelial cells may be found throughout pars nervosa. Cushing and Goetsch ('10) state that it is not uncommon in so-called normal human hypophyses, while Erdheim ('03) and Lucien ('09) found it more prevalent in advancing years.

Pars intermedia rarely comes to the external surface of the organ except at the most dependent point and of course along the hypophyseal stalk above pars anterior. Over half of its anterior border is separated from pars anterior by the residual lumen. There is a tendency for the intermediate lobe to surround the margins of this cavity and to form a little of its anterior wall. It extends some distance peripherally between pars anterior and pars nervosa beyond the hypophyseal cavity.

As is almost universally the case among animals, this part of the hypophysis is poorly provided with blood vessels. Almost no capillaries are seen in its interior. The posterior border is well supplied with vessels but they do not extend very far in the anterior.

The general histological features are shown in figure 4. It will be noted that four types of cells are present. The main bulk of the lobe is formed of cells which upon measurement (table 3) are seen to have about twice the volume of the cells of pars anterior. The abundant cytoplasm of these cells is devoid of many large granules and therefore, while rather basophilic in reaction, appears distinctly lighter than pars. anterior and hence its limits can be readily ascertained by almost any stain. These cells are irregular in shape due to mutual compression. The central cytoplasm is denser and contains more mitochondria than the peripheral cytoplasm (fig. 5 B), which has the general appearance of being composed of more fluid areas separated by denser strands radiating from the central cytoplasm. According to Lewis and Maurer ('20) the lighter areas between the denser strands are filled with secretory antecedents.

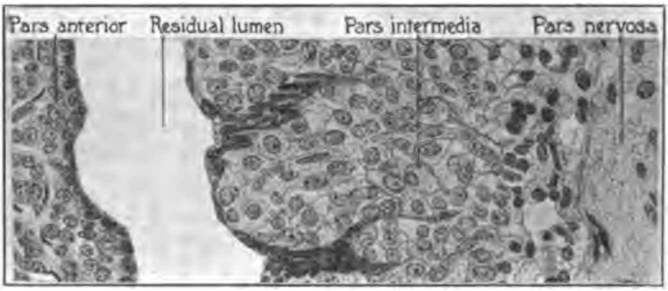

Fig. 4. Narrow strip through pars intermedia and a small part of adjacent pars anterior and pars nervosa. An enlarged view of the rectangular area outlined in figure 1. Formalin-corrosive sublimate fixation; methylene blue-eosin stain. X 400.

The nucleus is usually eccentric in position, rather vesicular in appearance and round or more or less elongated in shape.

Along the posterior margin a variable number of cells occur which are much smaller and contain much denser cytoplasm and a heavier staining nucleus. They are responsible for the darker shading along the posterior boundary of pars intermedia in figure 1. In figure 4 their hyperchromatic nuclei are best seen while figure 5 C is a sketch of three of these cells under higher power. The scanty cytoplasm is rich in mitochondria. The stratum which these cells form is not usually as wide as in the case illustrated in figure 4. It is as a rule more irregular in thickness, not being seen at all in places and in other limited areas being one-third as wide as the entire thickness of pars intermedia.

The anterior margin, which forms the posterior wall of the hypophyseal cavity, is lined by cells which may be either greatly flattened or high columnar as shown in figures 4 and 5 A. The columnar cells form groups which extend a variable distance into the substance proper—a great exaggeration of the tendency shown by Cooper ('19, fig. 4 B) in the California ground-squirrel. Protoplasmic trabeculae appear to project far beyond the deepest nuclei but gradually diminish in size till beyond recognition. Long spindle-shaped cells, sometimes reaching through the entire thickness of pars intermedia, have been observed in several other species (Herring '08). At the surface where the columnar cells become continuous with the flattened cells, transitional forms are found. Each trabeculum is marked by a depres-

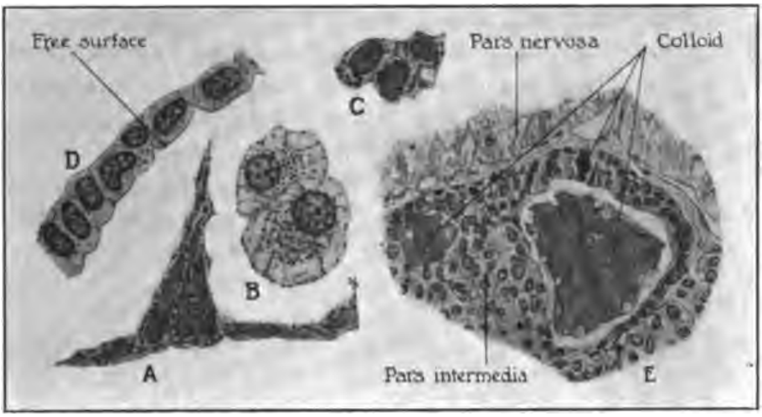

Fig. 5. Details from pars intermedia. The four small groups of cells show the mitochrondria of the different types of cells: A, typical cells lining the residual lumen and a trabeculum of long columnar cells which extend into pars intermedia; B, two typical cells forming the main bulk of pars intermedia; C, three small cells found next to pars nervosa; D, cells from the wall of a colloid-containing vesicle. Neutral formalin-potassium dichromate fixation; acid fuchsin-methyl green stain. X 1000. E, small area from pars intermedia and adjacent pars nervosa showing relation of colloid masses to surrounding tissue. Hematoxatin and eosin. X 265.

sion so that the anterior margin of pars intermedia is scalloped when seen in section (fig. 1).

The cytoplasm, though very scanty in the columnar cells especially, is well provided with mitochondria (fig. 5 A). The nuclei of the columnar cells are long and spindle-shaped and very hyperchromatic.

Another type of cell is found associated with the larger masses of colloid, which appears more or less abundantly. Occasionally a colloid mass is seen which is larger in diameter than the thickness of the entire juxtaneural lobe. Such accumulations as are shown in figure 5 E are more common. The larger masses contain a series of vacuoles around the margin (fig. 5 E). These are most likely the effects of some of the reagents. While the smaller colloid bodies are surrounded by the usual type of cell as if they had accumulated in intercellular spaces, the larger ones are surrounded at least partly by what appears to be a special epithelium. This epithelial wall is usually a single layer of cells but in places may consist of a double layer. An incomplete wall is seen in the largest vesicle in figure 5 E. The cells vary in shape from squamous to columnar. They are much smaller than the majority of the cells in pars intermedia. The cytoplasm is more homogeneous in appearance and, as pointed out by Lewis and Maurer ('20) in the pig, is very poor in mitochondria (fig. 5 D). The nucleus has a dense reticulum containing many large blocks of chromatin. Small masses of colloid may be found either in the cells or between them (fig. 5 E). These colloid cysts are not to be confused with the detached portions of the residual lumen mentioned by Vanderburgh ('17) in the guinea pig.

e. Residual lumen

A distinct residual lumen (hypophyseal cavity) is always present. It frequently contains colloid. While in general its outline is regular, it may be broken up at the margins by a fusion of its walls. As a result of this, small detached acini-like structures with high columnar cells and almost invariably containing colloid may be found between pars intermedia and pars anterior beyond the lateral borders of the main cavity. It is possible that some of the acini occasionally described in pars anterior as having columnar cells and a lumen containing colloid are similarly detached portions of the hypophyseal cavity. In the woodchuck the columnar cells forming the wall of the detached cavities are identical with those found in groups or trabeculae along the posterior wall of the main cavity; but, unlike the guinea pig's hypophysis (Vanderburgh '17), there are no cilia. When some of these outlying acini are followed in serial sections, they are found to communicate with the main lumen. Others have been completely cut off. As already mentioned, in rare instances the cavity may extend into pars nervosa along with the invading masses of pars intermedia cells. The residual lumen does not extend up along the infundibular stalk. No cilia were ever seen with certainty projecting into the cavity. It is surprisingly free from cellular debris.

f. During hibernation

In comparing the hypophysis as above described, which may be taken as the condition existing in the autumn before hibernation, with those taken from dormant animals, the difference, if any, was so slight that nothing short of careful volumetric analysis could be relied upon. Any unusual feature found during winter sleep could usually also be found in non-hibernating ones. There seemed to be nothing that was characteristic of the hypophysis during dormancy. The hyperchromatic and pycnotic character of the nuclei, described as being typical of the hibernating state, was found only here and there and was just as evident before lethargy. Methylene blue was purposely introduced to give a sharper nuclear stain but neither this nor hematoxylin, to say nothing about the other stains, brought out any difference. Nor was there any apparent difference in the average size of the cells. Limited regions were found in pars anterior of all the animals where the cells were smaller than usual. These areas are so irregular that no general examination warranted any statement as to the relative number of cells involved. The cells of pars anterior in the neighborhood of pars intermedia and the residual lumen invariably are smaller than the average. On the other hand, cells on the outer margin are slightly larger. This was true of all the animals and not merely in those hibernating, as one would infer from Cushing and Goetsch ('15). Judging from the area and number of sections the whole organ did not seem particularly smaller during hibernation, as has been reported, when the body weight was taken into consideration.

g. Post-hibernating period

There was, however, an unmistakable difference in several particulars between the hypophyses taken in the spring, after resumption of activity, and those taken from dormant animals and from animals killed before the onset of winter-sleep. These variations, together with the general similarity between lethargic and pre-lethargic animals, can best be demonstrated by a consideration of the results obtained by the volumetric study carried out. It might be stated here, however, that no evidence of cell division was seen in any case, notwithstanding the fact that such has been seen by Gemelli and by Cushing and Goetsch during the post-hibernating period and that the material here used was fixed instantaneously *in situ* immediately after death. Washing out the blood before perfusing with the fixer is a possible though not very probable explanation of this negative result.

TABLE 1.

Volumetric data on the whole hypophysis and its three principal parts before, during and after hibernation in the woodchuck.

Animal			Av.—Average Mi.—Minimum Ma.—Maximum	Whole Hypophysis		Percentage of Whole Hypophysis Formed by		
Number Involved	Number of Each Sex	Rectal Temperature °C.		Volume cc.	Percentage of Maximum Gross Body Weight	Pars Anterior (Distalis)	Pars Intermedia (Juxta-neuralis)	Pars Nervosa (Processus Infundib.)
BEFORE HIBERNATION								
9	4 Female 5 Male	35 to 38	Av. Mi. Ma.	0.00633 0.00545 0.00750	0.000235 0.000161 0.000280	47.2 40.6 50.7	2.41 0.97 3.84	50.4 45.5 56.3
DURING HIBERNATION								
9	4 Female 5 Male	7 to 16	Av. Mi. Ma.	0.00641 0.00542 0.00741	0.000235 0.000198 0.000291	44.9 34.6 50.6	2.51 1.05 3.71	52.6 45.9 63.2
AFTER HIBERNATION—NOT FED								
9	4 Female 5 Male	34 to 37	Av. Mi. Ma.	0.00865 0.00488 0.01099	0.000322 0.000222 0.000380	43.7 38.4 49.7	2.76 1.60 3.56	53.5 47.0 59.3
AWAKE SEVERAL WEEKS—FED ONE, TWO OR THREE WEEKS								
3	2 Female 1 Male	36 tc 38	Av. Mi. Ma.	0.00722 0.00500 0.01027	0.000312 0.000267 0.000353	45.6 37.5 53.7	2.51 1.80 3.21	51.9 44.5 59.2

VOLUME OF THE PRINCIPAL PARTS OF THE HYPOPHYSIS

a. Before Hibernation

The results of the volumetric analysis of the parts of the hypophysis of thirty animals with related data are tabulated in table 1. The volume of the whole hypophysis is merely the sum of the three principal parts which are listed in the last three columns. The average of the nine hypophyses obtained before hibernation was 0.00633 cc. Rather than making an extensive table with individual volumes, the condensed tabulations include only the smallest and the largest organ encountered in addition to the average, in order to indicate the range of individual variation. These limits happen to be very narrow in this group (0.00545 to 0.00750). It must be remembered that these volumes refer to the fixed material and therefore represents only about half of the real volume (Jackson '17). Since the hypophyses of the larger animals are, as a general rule, larger than those of the smaller animals, it is necessary to take into account the size of the animal. This has been done by placing in the next column the percentage of the body which is represented by the organ, assuming that its specific gravity is 1. This averages 0.000235 per cent, but there is an enormous individual variation (0.000161 to 0.000280). Although such marked variations have been noted in other animals (Hatai '13a, Jackson '17, and others) as well as in man, one source of error here is the necessity of taking the gross (and not the net) body weight. From over a hundred woodchucks in which the writer has determined the gastro-intestinal contents it may be said that the gross body weight includes anywhere from 1 to 10 per cent of such contents . But this seemed unavoidable because the essential point to determine was to what extent the hypophysis was modified by hibernation and by the restoration of activity, etc., but during this time the body weight is decreasing from lack of food and water till at the time of awakening 25 to 30 per cent has been lost.

The body weight was obtained in the fall before hibernation by weighing the living animal on a spring scale. Those that were kept in captivity for some time were weighed several times before dormancy set in. Each animal was ear-marked with a punch so as to be identified. Although many of the animals were kept under conditions which were almost identical with the normal habitat (Rasmussen '15), some lost and others gained weight while being fed in the fall before hibernation. Therefore, the maximum body weight obtained while active was used in making the calculations listed in tables 1 and 2. Nearly all the animals weighed between 2000 and 3000 grams.

From the last three columns in table 1 it is seen that the glandular portion (pars anterior and pars intermedia) constitute about half of the organ and pars nervosa the other half. Pars anterior varies from 40.6 to 50.7 per cent, average 47.2 per cent. Pars intermedia represents only 2.41 per cent on the average, but varies enormously (0.97 to 3.84 per cent). As will be shown in table 2, this variation is largely due to a sex difference. The females have a much smaller pars intermedia, but since the number of animals of a particular sex is the same in each of the three principal groups, this does not invalidate seriously a comparison of averages based on both sexes in these groups.

When compared with the only other data which have been found on the proportion of the whole organ formed by the principal components (Jackson '17, on the rat, Björkman '15, on the rabbit), it is found that pars anterior of the woodchuck constitutes about half and pars intermedia only about one-third the proportion that the corresponding parts represent in the hypophysis of the albino rat. On the other hand pars nervosa is more than six times the proportion found in the rat. In the rat, pars intermedia is as large as pars nervosa and each constitutes about 7½ per cent of the whole organ. In the rabbit, the proportions are much like those in the rat in that pars anterior constitutes by far the greatest bulk (66-73 per cent); while pars nervosa represents from 14 to 19 per cent, and pars intermedia 10 to 15 per cent. Numerous comparative data on the size of the hypophysis are given by Livon '09, but these refer only to the organ as a whole.

b. *During hibernation*

The figures obtained from the nine dormant animals are in every particular essentially like those from animals killed before hibernation. All are well within probable errors when individual variations and the limited number of animals are taken into consideration. If the percentage which the organ formed of the body weight had been calculated from the weight of the animal when killed, the hypophysis would have appeared to be about 25 per cent larger than is characteristic of the pre-hibernating stage, hence the necessity of knowing the original weight before emaciation sets in. It is reasonably certain, therefore, that the hypophysis does not diminish in size during hibernation in the woodchucks here investigated.

c. *After hibernation*

In comparison with the two preceding groups this third group, which consists of animals that had been awake from several days to several weeks with no food available, shows an increase of fully one-third in the size of the hypophysis. The whole gland varies from 0.000222 to .000380 per cent of the maximum gross body weight, average 0.000322. This agrees with the findings of Gemelli and of Cushing and Goetsch. There is not enough variation from the above two groups in the relative proportion of the lobes to indicate any particular difference in the rate of hypertrophy of the three parts. If anything, pars nervosa has increased slightly more than pars anterior—just the reverse of what one would expect from the supposed decrease in the latter pictured by previous investigators.

The reason for this general hypertrophy has already been suggested earlier in this article where reference was made to increased activity especially in the sex gland during the rutting period and the interrelation of the hypophysis and gonads. The great variation in pars intermedia is again largely due to a sex difference.

Attention should be drawn to the difference in the effects of inanition in this hibernating species of rodent even when active and in the albino rat, a non-hibernating rodent. Jackson ('17) found in the adult that inanition produced generally a relative decrease in pars anterior with evidence of atrophy and degeneration. In all probability animals that regularly hibernate have a degree of resistance to inanition and other conditions such as is not generally found. The storage of an enormous amount of fat and the great reduction in oxidation readily suggest that inanition effects during dormancy would be largely obviated; but it is rather strange that upon waking up and becoming active after one-fourth or more of the body weight has been lost, there are no inanition effects even after three or four weeks deprivation of food and water with rapid loss of body weight.

The last group of three animals, fed one, two or three weeks respectively after having been awake several weeks without food, do not differ essentially from those that had not been fed. It is evident that the hypertrophy of the hypophysis during the rutting season goes on independently of the food factor.

d. Sex differences

The volumetric data on the lobes brought out the fact that there is a fairly constant sex difference. To show this more clearly, all the females were grouped together and an equal number of males so that there were as many males as females from each of the four groups or stages. The results are tabulated in table 2. It appears from this that the male gland is about 13 per cent heavier than the female when the 6.4 per cent difference in body weight is taken into account. Similarly each lobe is larger in the male. Pars nervosa follows closely the whole organ but pars anterior is only about 10 per cent larger in the male. It is pars intermedia, however, that is markedly different in the two sexes, being 50 per cent larger in the male than in the female of the same body weight. Of the 13 females only one had a gland near the upper limits and of the males only one had a gland near the lower limit.

TABLE 2.

Sex differences in the hypophysis of the woodchuck based on 13 males (average body weight—2638 grams) and 13 females (average body weight—2480 grams). Males 6.4 per cent heavier than the females.

Sex	Whole Gland		Pars Interior		Pars Intermedia		Pars Nervosa	
	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight	Volume cc.	Per cent of Body Weight
Male	.00734	.000278	.00348	.000132	.00022	.0000083	.00365	.000138
Female	.00614	.000248	.00296	.000120	.00014	.0000056	.00303	.000122
	Larger in Male than in Female by 19.5 per cent		Larger in Male than in Female by 16.9 per cent		Larger in Male than in Female by 56.8 per cent		Larger in Male than in Female by 20.4 per cent	

In albino rats above 50 grams in weight the females have a larger hypophysis than the males (Hatai '13a). Jackson ('17) finds that this is chiefly, if not entirely, due to a larger pars anterior. His figures on pars intermedia, however, indicate, if anything, that it is slightly larger in the male. Wittek ('13) found that in cattle the hypophysis is also relatively larger in the female. In the human species (Caselli '00, Lucien '11) the female hypophysis is apparently slightly larger, especially as percentage of body weight and the same seems to be true of the rabbit (Björkman '15).

Pregnancy, which may cause enlargement of the hypophysis (Comte '98, Erdheim and Stumme '09 and others), is no complicating factor in the animals used for this study since the woodchuck does not breed in captivity. All the reproductive organs of these animals were carefully examined and fixed for other studies and no cases of pregnancy were found.

TABLE 3.

Volumetric data on the parenchyma cells of pars anterior and pars intermedia of the hypophysis of the woodchuck before, during and after hibernation. All figures in micra. Same animals in the various groups as in Table 1.

Av.—Average Mi.—Minimum Ma.—Maximum	PARS ANTERIOR				PARS INTERMEDIA			
	WHOLE CELL		NUCLEUS		WHOLE CELL		NUCLEUS	
	Volume	Diameter	Volume	Diameter	Volume	Diameter	Volume	Diameter
BEFORE HIBERNATION								
Av. Mi. Ma.	854.2 791.9 922.8	11.8 11.4 12.5	84.9 76.0 88.2	5.45 5.25 5.52	1790.8 1524.5 2017.6	15.1 14.0 16.0	108.5 103.3 119.0	5.92 5.82 6.10
DURING HIBERNATION								
Av. Mi. Ma.	860.3 814.5 1098.1	11.8 11.6 12.8	90.7 83.5 100.8	5.57 5.42 5.77	1889.9 1319.3 2503.7	15.3 13.0 17.4	108.8 105.5 131.1	5.92 5.86 6.30
AFTER HIBERNATION—NOT FED								
Av. Mi. Ma.	847.5 671.3 1005.2	11.7 10.8 12.4	92.1 81.2 105.1	5.60 5.37 5.86	2332.5 1932.5 2835.0	16.6 15.0 18.0	118.8 103.4 132.6	6.10 5.88 6.33
AWAKE SEVERAL WEEKS—FED ONE, TWO OR THREE WEEKS								
Av. Mi. Ma.	881.1 814.5 915.0	11.9 11.6 12.0	96.0 94.4 97.4	5.68 5.65 5.71	1668.4 1501.4 1790.8	14.7 14.2 15.0	111.7 102.5 121.1	5.97 5.81 6.14

SIZE OF CELLS AND NUCLEI IN PARS BUCCALIS

a. Pars anterior

The result of the volumetric study of cells and nuclei of thirty animals are collected in table 3. With reference to pars anterior before hibernation it is seen that the average cell diameter is 11.8 μ and the average volume is 854.2 cu. μ. The nuclei average 5.45 μ in diameter and 84.9 cu. μ in volume. During hibernation these figures are not decreased, being the same for the cell and slightly larger for the nucleus. Similarly after hibernation and before feeding there is but little change in the size of the whole cell (a decrease, if anything, but too slight to be of any significance), but the nucleus apparently slowly increases. There are so few animals in the last group that the effect of feeding is not established.

The atrophic changes during hibernation described by Gemelli and by Cushing and Goetsch are not supported by these measurements, nor do the cells as a whole seem to get larger after becoming active in the spring.

The inanition effects described by Jackson ('17) in the rat (reduced and vacuolated cytoplasm, hyperchromatism and pycnosis of the nucleus). are not in evidence in the emaciated woodchuck.

b. Pars intermedia

The cells in pars intermedia (excluding the smaller cells, with hyperchromatic nuclei and located in the posterior portion and also excluding the cells lining the residual lumen) are about twice the size of the cells of pars anterior. The nuclei are also larger being nearly 6 μ in diameter as compared with 5.5 μ, the diameter of pars anterior cells. Here again there is no difference between the pre-hibernating period and that of dormancy. The third, or post-hibernating group, shows a perceptible increase in the size of both cells and nuclei. This, however, is not supported by the three fed animals in the last group.

TABLE 4.

Relative number of acidophilic and basophilic cells in pars anterior of the woodchuck hypophysis based on counting from 206 to 284 fields in each of four animals (2 males and 2 females) in each of the three groups. Figures refer to the number of cells per field.

The headings below refer to the averages obtained from ndividual animals.	BEFORE HIBERNATION		DURING HIBERNATION		AFTER HIBERNATION	
	Acido.	Baso.	Acido.	Baso.	Acido.	Baso.
Average of all four animals.........	36.3	4.5	40.6	4.7	46.9	14.7
Minimum.........................	33.8	1.1	38.5	4.0	40.3	12.6
Maximum.........................	39.2	12.7	44.6	4.9	54.4	16.7

RELATIVE NUMBER OF ACIDOPHILES AND BASOPHILES IN PARS ANTERIOR

a. Before hibernation

To check the assertion that during hibernation there is a loss of the differential staining power of the cells in pars anterior, the average number of acidophiles and basophiles present in a microscopic field was determined in two males and two females from each of the three principal groups. These data, as filed in table 4 show that before hibernation there were 36.3 acidophiles and 4.5 basophiles per field. The basophiles varied between such wide limits (1.1 and 12.7) that the average is not worth much. The mean value was, of course, lower than the average.

b. During hibernation

The figures obtained during hibernation do not vary much from those already given. The range of variation was much more limited in the case of the basophiles, while the acidophiles are slightly more numerous. Dormancy, therefore, produces no striking modification in the number of chromophilic cells which appear as a rule at least as numerous during hibernation as before. One case was found to contain three times as many basophiles before as was ever found during lethargy but the rest had distinctly fewer. The intensity of the differential stain was as great as was generally the case in the preceding group.

c. After hibernation

After waking up a marked increase in the number of basophiles is indicated (14.7 as compared with 4.7 during and 4.5 before hibernation). There appears to be only a slight increase in acidophiles. Since the anterior lobe is a third larger at this time (table 1), the total numerical increase is unquestionable—amounting to about four times in the case of the basophiles. This increase in chromophile cells fully accounts for the enlargement of the pars anterior. The basophiles also stain more strongly with the basic dyes so that they stand out more prominently. The macula is therefore more evident in thin sections and the whole Golgi apparatus—if such it is—is generally larger than at any other time. The increased differential staining properties of the basophiles is fully in accord with all previous observations. It cannot be said that the acidophiles stain more intensely.

Here again the decrease in the specific staining reaction noted by Jackson ('17) in the rat during inanition is not duplicated in starving woodchucks with a loss in body weight from 30 to 40 per cent, in round numbers (Rasmussen and Rasmussen '17, p. 141).

d. Significance of the different types of cells in pars anterior

The many writers that have commented on the significance of the different types of cells in pars anterior (for literature Biedl '16, Schäfer '16, Cooper '19) may be classified into two main groups. Probably a majority (St. Remy, Benda, Caus and Van der Stricht, Herring, Stendell, Pirone, Launois, Thaon and Joris, Sandri, Noronha, Vanderburgh, Cooper and others) favor the view that they are merely different functional stages of the same general type of cell. The basophilic are generally regarded as containing the ripe secretion and the other types as being in earlier stages of the secretory process. The other group (Lothringer, Rogowitsch, Stieda, Flesch, Gemelli, Scoffidi, Thom, Guerrine, Erdheim, Kon, Kraus, Schäfer, Addison, etc.) believe they represent at least two different functional types, there being a strong tendency to favor the derivation of the chromophiles from the chromophobes, but to consider the acidophiles and basophiles as functionally different; but ideas vary greatly.

The almost total lack of intermediate forms, particularly between the acidophiles and basophiles, as judged after staining with a differential stain such as Mallory's acid fuchsin—aniline blue—orange G, does not favor the view that the three kinds of cells are different functional stages of the same cell. In the very active rutting period when the hypophysis enlarges, one would from the first theory expect to see many transitional forms.

The lack of any modification of the general cell picture during profound dormancy in the woodchuck leaves us with no positive suggestion from this source as to the functional significance of any of the constituents of the hypophysis; but the marked response to increased activity shown by the basophilic cells, indicates that this type is more intimately related to processes which are readily influenced by the changed conditions incident to hyperactivity. The susceptibility of the basophiles is also shown by the increase in size, number and vacuolization which they undergo in the albino rat after castration (Addison '17a). Although the acidophiles also are affected by ovariotomy in the human female, Rössle ('14) noted as well a decrease and even lack of basophiles. Possibly in time the greatly modified basophiles pictured by Addison in the rat would become so necrotic as to be absorbed, thus bringing the above two observations into substantial agreement. According to Lucien ('11) there is a marked increase in the basophilic cells in the aged and Raeder ('20) reports that in the feeble-minded, where the hypophysis is involved more often than any other ductless gland, the most frequent change is a deficiency of the basophilic cells.

Until the appearance of the different cells during specific stages of their activity is more fully known it is hazardous to attempt any elaborate interpretation of the findings here reported.

SUMMARY

1. The hypophysis cerebri of the woodchuck has all the structures generally recognized. The processus infundibuli and the distal portion of the infundibulum are solid. There is a well preserved residual lumen. The whole organ (after fixation and embedding) forms normally 0.000235 per cent of the gross body weight.

2. Pars anterior (distalis) forms a crescentic lobe which constitutes 46 per cent of the entire organ before and during hibernation. It has the usual rich blood supply. Three types of cells are recognized in this lobe: chromophobes, acidophiles and basophiles. The lack of intermediate forms (tinctorially) militates against the theory that these three types are only different functional stages of the same cell.

3. Pars intermedia (juxta-neuralis) represents only 2.46 per cent of the whole gland (average of pre-hibernating and hibernating stages). The great bulk of this structure is composed of the usual large cells. An irregular stratum of smaller cells forms the posterior boundary. The cells next to the residual lumen are greatly modified into squamous and into long spindle-shaped columnar cells. Colloid is frequently abundant—the larger masses being partly or entirely surrounded by a wall of special cells.

4. A sex difference is apparently revealed by the volumetric analysis of the lobes. The male gland averages 13 per cent larger than the female. This difference is equally shared by pars nervosa and pars buccalis (glandularis), but of the two components of the latter pars intermedia is 50 per cent larger while

pars anterior is only 10 per cent larger in the male. However, only 26 animals (13 males and 13 females) are considered.

5. Hibernation produces no change in the weight or histological structure of the hypophysis when compared with the pre-hibernating gland, which is the standard of greatest reliance. The atrophic appearance of pars anterior (suggesting a stage of hypofunction) as previously reported is not confirmed.

6. Immediately after waking up in the spring, during the rutting season, hypertrophy takes place in the hypophysis amounting to 33 per cent in animals kept in captivity. This is distributed proportionately among the three principal parts of the gland. The chief cells and their nuclei in pars intermedia apparently increase slightly in size. While the average volume of the cells in pars anterior shows no variation, the nuclei show a little enlargement. The conspicuous change accompanying the heightened activity is a tripling of the relative number of basophiles and a distinct increase in their staining reaction.

7. It is believed that a failure to compare the hypophysis of the hibernating stage with that of the stage just before the onset of dormancy and the tendency to interpret the post-hibernating conditions as the normal state, are responsible for the idea that winter-sleep in the marmot produces atrophic changes. The return to the pre-hibernating condition evidently occurs late in the summer after the active stage of the sexual cycle has terminated, as is the case with the interstitial cells of the testis and ovary. The limited number of animals involved and the great range of individual variation are also probable sources of error which are to some extent applicable to this study as well.

8. There is a striking difference in the reaction of the woodchuck and of the albino rat (a non-hibernating species) to inanition. While inanition in the rat produces atrophic changes in the hypophysis (Jackson), starvation even in the spring during several weeks of activity and after three months deprivation of food during dormancy, is attended with no such characteristics but rather with hypertrophy of the whole organ and hyperplasia of some of its elements.

I wish to express my appreciation of the valuable assistance rendered by Dr. Sutherland Simpson (Cornell University, Ithaca, N. Y.) in the securing of material and by Dr. C. M. Jackson in connection with the volumetric methods and in the form of many other suggestions. Credit is also due Mr. G. H. Childs for the careful preparation of the illustrations.

BIBLIOGRAPHY

Addison, W. H. F.: 1917a. The cell-changes in the hypophysis of the albino rat, after castration. J. Comp. Neur. (Phila.), **28**, 441.

——: 1917b. The Golgi apparatus in the cells of the distal glandular portion of the hypophysis. Anat. Rec. (Phila.), **11**, 317.

Allen, B. M.: 1920. Experiments in the transplantation of the hypophysis of adult Rana pipiens to tadpoles. Science (Garrison, N. Y.), n.s., **52**, 274.

Bell, W. Blair: 1919. The pituitary: a study of the morphology, physiology, pathology and surgical treatment of the pituitary, etc. William Wood and Co., New York.

Biedl, Artur: 1916. Innere Sekretion, 3 Auflage, II Teil, pp. 82 and 674.

Björkman, H.: 1915-16. Bidrag till hypofysens aldersanatomi hos kaninen. Upsala Läkareförenings Förhandlingar, N. F., **21**, 49.

Caselli, A.: 1900. Studii anatomici e sperimentali sulla fisiopathologia della glandola pituitaria. Reggio Emilia (cited by Biedl).

Comte, L.: 1898. Contribution à l'étude de l'hypophyse humaine et de ses relations avec le corps thyroide. Beitr. z. path. Anat. u. z. allg. Path. (Weisbaden), **23**, 90.

Cooper, H. J.: 1919. The hypophysis cerebri of the California ground squirrel, Citellus beechyi (Richardson). Am. J. Anat. (Phila.), **26**, 185.

Cowdry, E. V.: 1916. The structure of chromophile cells of the nervous system. Contributions to Embryology, vol. 4 (Publication No. 224, Carnegie Institution, Washington), No. 11, p. 27.

Cushing, H., & Goetsch, E.: 1910. Concerning the secretion of the infundibular lobe of the pituitary body and its presence in the cerebro-spinal fluid. Am. J. Physiol. (Balt.), **27**, 60.

——: 1913 Hibernation and the pituitary body. Proc. Soc. Exper. Biol. & Med. (N. Y.), **11**, 25.

——: 1915. Hibernation and the pituitary body. J. Exper. M. (N. Y.), **22**, 25.

Dana, C. L.: 1916. Morbid somnolence and its relation to the endocrine glands. Med. Rec. (N. Y.), **89**, 1.

Erdheim, J.: 1903. Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und Hypophysis. Beitr. z. path. Anat. u. z. allg. Path. (Weisbaden), **33**, 158.

Erdheim, J., & Stumme, E.: 1909. Über die Schwangerschaftsveränderung der Hypophyse. Beitr. z. path. Anat. u. z. allg. Path. (Weisbaden), **46**, 1

Gemelli, A.: 1906. Sul'ipofisi delle marmotte durante il letargo e nella stagione estiva; contributo alla fisiologia dell'ipofisi. Arch. per le sci. med. (Torino), **30**, 341; Reale Ist. Lomb. di sci. e lett. Rendic. (Milano), s. 2, **39**, 406.

——: 1906. Nuove osservazioni su l'ipofisi delle marmotte durante il letargo e nella stagione estiva; contributo alla fisiologia dell'ipofisi. Biologica (Torino), **1**, 130.

——: 1907. Les processus de la sécrétion de l'hypophyse des mammifères. Arch. ital. de biol. (Torino), **47**, 185.

Goetsch, E., & Cushing, H.: 1913. The pars anterior and its relation to the reproductive glands. Proc. Soc. Exper. Biol. & Med. (N. Y.), **11**, 26.

Goetsch, E.: 1916. The influence of pituitary feeding on growth and sexul development. Johns Hopkins Hosp. Bull. (Balt.), **77**, 29.

Hammar, J. A.: 1920. A plea for systematic research work in the anatomy, normal and morbid, of the endocrine system. Endocrinol. (Los Angeles), **4**, 37.

Hatai, S.: 1913a. On the weight of the abdominal and thoracic viscera, the sex glands, ductless glands and the eyeballs of the albino rat (Mus norvegicus albinus) according to body weight. Am. J. Anat. (Phila.), **15**, 87.

——: 1913b. The effect of castration, spaying or semi-spaying on the weight of the central nervous system and of the hypophysis of the albino rat; also the effect of semi-spaying on the remaining ovary. J. Exper. Zool. (Phila.), **15**, 297.

——: 1915. The growth of organs in the albino rat as affected by gonadectomy. J. Exper. Zool. (Phila.), **18**, 1.

Hayami, T.: 1919. On the relation between the interstitial cells and the hypertrophy of the hypophysis. Verhandl. d. jap. path. Gesellsch. (Tokyo), 1919, **43**.

Herring, P. T.: 1908. The histological appearance of the mammalian pituitary body. Quart. J. Exper. Physiol. (Lond.), **1**, 121.

Hill, R. L.: 1916. Some aspects of the physiology of milk secretion. J. Am. Veter. M. Ass. (Ithaca, N. Y.), July, 1916.

Hoskins, E. R.: 1916. The growth of the body and organs of the albino rat as affected by feeding various ductless glands (thyroid, thymus hypophysis and pineal). J. Exper. Zool. (Phila.), **21**, 295.

Houssay, B. A.: 1918. La accion fisiologica de los extractos hipofisiarios. Buenos Aires.

Howell, A. H.: 1915. Revision of the American marmots. North American Fauna, No. 37, U. S. Department of Agriculture, Bureau of Biological Survey, Washington, D. C.

Jackson, C. M.: 1917. Effects of inanition and refeeding upon the growth and structure of the hypophysis in the albino rat. Am. J. Anat. (Phila.), **21**, 321.

——: 1919. The postnatal development of the suprarenal gland—and the effects of inanition upon its growth and structure in the albino rat. Am. J. Anat. (Phila.), **25**, 221.

Lewis, D. D., & Maurer, S.: 1920. Secretion antecedents in the cells of the pars intermedia of the hypophysis of the pig. Anat. Rec. (Phila.), **18**, 238.

Livingston, A. E.: 1916. The effect of castration on the weight of the pituitary body and other glands of internal secretion in the rabbit. Am. J. Physiol. (Balt.), **40**, 153.

Livon, Ch.: 1909. Quelques données sur les dimensions et le poids de l'hypophyse. Marseille Méd, **46**, 683.

Lucien, M.: 1909. Les cellules cyanophiles du lobe posterieur de l'hypophyse humaine. Compt. rend. Soc. d. biol. (Paris), **67**, 743.

——: 1911. Le poids, les dimensions et la forme générale de l'hypophyse humaine aux différents ages de la vie. Compt. rend. Assoc. Anat. (Paris), Réun. 13, p. 147.

Mann, F. C.: 1916. The ductless glands and hibernation. Am. J. Physiol. (Balt.), **41**, 173.

Raeder, O. J.: 1920. Endocrine imbalance in the feebleminded. J. Am. M. Ass. (Chicago), **75**, 527.

Rasmussen, A. T.: 1915. The oxygen and carbon dioxide content of the blood during hibernation in the woodchuck (Marmota monax). Am. J. Physiol. (Balt.), **39**, 20.

——: 1916. Theories of hibernation. Am. Naturalist (N. Y.), **50**, 609.

——: 1917. Seasonal changes in the interstitial cells of the testis in the Woodchuck (Marmota monax). Am. J. Anat. (Phila.), **22**, 475.

——: 1918. Cyclic changes in the interstitial cells of the ovary and testis in the woodchuck (Marmota monax). Endocrinol. (Los Angeles), **2**, 353.

——: 1919. The mitochondria in nerve cells during hibernation and inanition in the woodchuck (Marmota monax). J. Comp. Neur. (Phila.), **31**, 37.

Rasmussen, A. T., & Myers, J. A.: 1916. Absence of chromatolytic changes in the central nervous system of the woodchuck (Marmota monax) during hibernation. J. Comp. Neur. (Phila.), **26**, 391.

Rasmussen, A. T., & Rasmussen, G. B.: 1917. The volume of the blood during hibernation and other periods of the year in the woodchuck (Marmota monax). Am. J. Physiol. (Balt.), **44**, 132.

Rössle, R.: 1914. Das Verhalten der menschlichen Hypophyse nach Kastration. (Virchow's) Arch. f. path. Anat. u. Physiol. u. f. klin. Med. (Berl.), **216**, 248.

Salmon, A.: 1905. Sull' origine del sonno. Studio delle relazioni tra il sonno e la funzione della glandula pituitaria. Firenze.

——: 1910. Le sommeil pathologique; l'hypersomnie. Rev. de méd. (Paris), **30**, 765.

——: 1910. La function du sommeil—physiologie, psychologie, pathologie. Paris. (See also Lo Sperimentale, 1916, **70**, 345.)

Saito, T.: 1919. A biological study of the hypophysis. Sei-I-Kwai M. J. (Tokyo), **38**, 328 (abstracted in Endocrinol., **4**, 467).

Schäfer, Edward A.: 1916. The endocrine organs. Longmans, Green and Co., Lond. & N. Y.

Stelwagen, T. E., Jr.: 1916. Anterior pituitary therapy in impotence in the male, a preliminary report. N. York M. J. (N. Y.), **103**, 879.

Tilney, F.: 1911. Contribution to the study of the hypophysis cerebri with especial reference to its comparative histology. Memoirs of The Wistar Institute of Anatomy and Biology, No. 2, Philadelphia.

——: 1913. An analysis of the juxta-neural epithelial portion of the hypophysis cerebri, with an embryological and histological account of a hitherto undescribed part of the organ. Internat. Monatschr. f. Anat. u. Physiol. (Leipzig), **30**, 258.

Vanderburgh, C. M.: 1917. The hypophysis of the guinea pig. Anat. Rec. (Phila.), **12**, 95.

Vincent, Swale: 1912. Internal secretion and the ductless glands. New York and London, p. 368.

Wittek, Josef: 1913. Ueber das Verhalten der Rinderhypophyse bei den verschiedenen Geschlechtern in der Gravidität und nach der Kastration. Arch. Anat. u. Physiol. (Leipzig), 1913, Anat. Abt., Suppl.-Bd., p. 127.

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ON THE ORGANIZATION OF NEURO-ANATOMY FOR MEDICAL STUDENTS UPON A THOROUGH-GOING FUNCTIONAL BASIS WHERE ONLY THE HUMAN BRAIN IS USED FOR DISSECTION

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SIX FIGURES

The report of the proceedings of the thirtieth annual meeting of the Association of American Medical Colleges shows that there still exists great diversity in the methods used in connection with the course in neuro-anatomy. The efficient teaching of this important and difficult course is undoubtedly one of the real problems before the medical schools. This is largely because of the complex nature of the subject and the limited time allowed for its study. The most economical utilization of the student's time is also becoming extremely important throughout the entire medical curriculum, due to the expansion and increased technicality of the subject-matter. On this account any suggestions for improvement which appear to develop as a result of the application of a particular method of handling a subject should be put on record that others may test it out. Too often a teacher is conducting a course as he was taught, irrespective of the efficiency of the method.

In connection with neuro-anatomy many valuable suggestions have appeared from time to time, such as the emphasizing of the functional aspect, methods of dissection which result in maximum exposure of internals tructures, construction of large fiber-tract models, providing students with outline sketches to aid them in their work on the brain stem, etc. These all have their place and should be available and utilized. What is intended here is to outline the course as it is now given at the University of Minnesota, in order to show the practicability of proceeding upon a thoroughgoing functional basis. It is believed that the method of approach here used has a number of features which contribute to the economical expenditure of the student's time and ultimately to greater clearness in the physiological and clinical significance of the great array of anatomical details, which are too often left as merely a bewildering complexity.

This course on the gross and microscopic anatomy of the nervous system and organs of special sense is the outgrowth of many years of teaching and research by Dean J. B. Johnston (whose functional attitude and numerous publications in neurology are well known, in particular see "A new method of brain dissection," Anat. Rec., vol. 2, p. 345, 1908) together with a number of minor modifications which seemed advisable to the writer after twelve years of experience with neurology in several universities.

Since only human brains are used for dissection, the approach to various structures must be carefully planned and plainly indicated to avoid undue destruction of things to be dissected later on in the course. It is not only possible, but practicable for each pair of students to get all the essentials upon one half of a human brain and have a respectable-looking dissection at the end of the course. It is, however, quite necessary to have available in the laboratory demonstration dissections and brains cut in gross serial sections in the vertical and in the horizontal plane. Such series wil last for several years if the individual sections are about a centimeter thick and each series kept together in a jar sufficiently large to permit easy removal of the brain by the students. Brains from bodies in which the blood vessels have been injected with coloring matter are often especially good for this purpose, even if they have dried up to some extent. There is frequently an excellent differentiation of the white and the gray matter due to the gray having taken up more of the pigment from the injection mass.

The general plan of the course, after an introductory survey of the meninges, external anatomy of the brain and spinal cord and the methods utilized in working out the architecture of the nervous system, is to take up in turn each of the great afferent conducting systems, commencing in each case with the receptors or end-organs, then reviewing the peripheral nerves and ganglia involved, and finally the fiber bundles and related gray matter in the spinal cord and brain to the highest known centers. As the tracts are followed upward in the central nervous system, the principal reflex connections encountered are indicated. After considering all the afferent systems except the olfactory—which is left till later in the course when the rhinencephalon can be most advantageously dissected—the cerebral hemispheres are taken up in the lectures under such headings as cause and significance of fissure formation, cerebral localization, histology of the cortex, association, commissural and projection fibers, while in the laboratory cerebral topography and histology of the cortex are considered and as much of the hemisphere dissected as is necessary to disclose the association, commissural and projection bundles. This prepares the students for taking up the efferent mechanism, although a general idea of the efferent limb of many reflex arcs has already been obtained incidentally in connection with the afferent system. The principal efferent systems are then traced to lower motor neurones whose relation to the peripheral nervous system and muscles and glands naturally follow. The olfactory system is then taken up. This leaves for final consideration the brain ventricles and the blood supply. Since during the course of dissection the blood vessels are not readily followed, demonstration specimens with vessels injected are used in the laboratory to elucidate the arterial supply and venous drainage.

Practically all anatomical structures are considered as they are encountered in following a conducting mechanism, and hence have a meaning which cannot be conveyed by merely stating that this is concerned with one function and that with another, which is about as far as many get along the line of functional analysis. Where the course is followed by a thorough review of the functional systems, the structures take on real meaning; but why not give the student this added interest while he is working out the structure? It is also believed that by this method there is obtained a better working knowledge of the inner architecture of the brain, because it is necessary to go up and down the brain stem several times, each time following a particular conducting chain of neurones. The method also automatically eliminates from the course unnecessary details.

Each laboratory period is preceded by a lecture which prepares the student for the practical work to follow. After the completion of a certain phase of the subject, a series of about twenty-five demonstration preparations are shown, supplementing the lecture and accompanied by notes or a fully labeled sketch or both as the case may demand. Each laboratory section is assigned a particular hour for studying these preparations. If there are at least as many specimens as there are students in a section so that each student can be kept busy, a surprisingly large amount of information is obtained by the student in an hour.

While some say that pathological material is not necessary, a very effective means of stimulating interest and at the same time a method of presenting facts that cannot be seen in normal specimens is to demonstrate the results of known pathological or experimental lesions. Series of Marchi and Weigert preparations of degenerated tracts arranged in proper sequence showing the position and extent of the most important fasciculi through the brain stem and spinal cord are almost necessary to convince some students that the specific conducting bundles that are mentioned actually exist. Experimental and pathological material stained by the Marchi method is especially valuable at the beginning of the course to show how it is possible to follow a tract a long distance even when greatly mixed with other fibers. In demonstrating a long tract, the cross-sections of various levels should be arranged in proper order and the students made to go from microscope to microscope in the direction of nerve conduction. And certainly the significance of the architecture of the normal nervous system can be emphasized in no better way before medical students than incidentally to call attention at the appropriate time to such things as syringomyelia and disassociated sensibility; degeneration of the dorsal funiculi and ataxia; equilibratory disturbances, nystagmus, etc., in vestibular and cerebellar lesions; types of blindness resulting from lesions in different parts of the optic mechanism; differences in motor disturbances in lesions at different levels of the pyramidal system, etc.

How the subject-matter can be arranged according to the above scheme to be given in three periods (total ten hours) per week during one quarter (twelve weeks) can best be seen from the following schedule. This assumes that it is not necessary to duplicate to any extent the embryology or general histology of nervous tissue, except in the form of demonstrations here and there in the course, which is especially the case where the neurology instructor handles the neural part of the regular courses in histology and embryology. We find it desirable to have the laboratory period on which the demonstration occurs three hours in length so as to leave two hours for regular laboratory work. On this period one laboratory section at a time is taken by the instructor into the demonstration room for one hour and then returned to the regular laboratory to allow the next section to come to the demonstration.

It is, of course, not practicable to have the lectures and laboratory work run exactly parallel throughout, since the time that can profitably be spent in lectures does not vary from subject to subject directly with the time necessary to cover the practical side. Thus the first time a long conducting system is followed through the brain stem, sufficient time must be allowed to get some of the prominent land-marks and make a limited number of outline sketches illustrating typical levels. Structures not directly involved in the system followed need not be sketched in detail nor at all if not readily recognized for the time being. Like the method advocated by Doctor Lineback for embryology and used by Doctor Herrick in neurology, details are added to these drawings as subsequent systems are considered. If the particular slides to be outlined are carefully selected for the student, seven sketches will usually suffice to show all the essential internal structures of medulla oblongata, pons, midbrain, and diencephalon, including the nuclei and root fibers of the cranial nerves. For convenience these seven levels above the spinal cord are numbered from 1 to 7, from below upwards. Each student's loan collection contains many intermediate levels (from 24 to 50), which he is expected to study. All the structures belonging primarily to a given system may be indicated, as is frequently done, by the use of a particular color.

The total number of sketches of microscopical preparations and of dissections required is twenty-eight. Copies of several charts are also called for. Naturally these must be made as simple as possible, for time does not permit the making of what some would call presentable drawings, and yet, as most agree, some sort of record seems desirable. There is, of course, no time for making microscopical preparations which students may claim as their own. Those who agree with Doctor Wells that students should come to pathology with a personal collection of normal preparations will have to show where more time is available for microscopic anatomy, since it is frequently a question of utilizing the available time in either making slides or in studying them. The statement that the loan collection is merely an easy way of getting around difficulties is unjustified in most cases, if not in all.

Two preliminary written examinations of one hour each are given during the course—one in the fourth week and another in the eighth week—sometimes in the lecture period and other times during a laboratory period, depending upon where the time can best be spared. Several short practical quizzes are given at irregular intervals. The final test consists of a two-hour written and a one-hour practical examination.

Quarterly schedule

PERIOD	LECTURE (1 HOUR)	LABORATORY AND DEMONSTRATION (2 OR 3 HOURS)
1	Meninges and meningeal spaces Gross Microscopic	Meninges, gross and microscopic Dem. 1—Meninges. Cytology of nerve cells, nerve fibers, and neuroglia
2	Neurological methods General morphological Methods involving nerve degeneration	External features of spinal cord and rhombencephalon (omitting, temporarily, details on cerebellar lobes and fissures)
3	Special histological (Cajal, Golgi, etc.) Physiological Pharmacological	External anatomy of mesencephalon and diencephalon Dem. 2—Degeneration and regeneration of nerve fibers
4	Pain, touch, and temperature system commenced Tactile corpuscles	External topography of the telencephalon
5	Peripheral nerves and ganglia involved and their structure	Spinal gang., microscopic structure Begin microscopic structure of the spinal cord
6	Spinal cord Microscopic structure Reflex possibilities	Spinal cord, microscopic structure Dem. 3—Sensory nerve endings, spinal ganglia, spinal cord
7	Conduction in spinal cord of pain, touch, temperature Spinal V. tract and its relation to Nn. V., IX., X.	Lower medulla oblongata (level 1) Microscopic structure with special reference to spinal lemniscus, spinal V. tract and its nucleus
8	Spinal and trigeminal lemnisci to the thalamus Internal capsule and Cortical areas related to pain, touch, temperature	Upper medulla oblongata (level 2) and Lower pons (level 3) Microscopic structure, special reference to pain, touch, temperature conducting system
9	Deep sensibilities (muscle sense, etc.) system commenced Muscle and tendon spindles Peripheral nerves involved	Pons at entrance of N. V. (level 4) Lower midbrain (level 5) Microscopic structure with special reference to pain, touch, etc.
10	Course within spinal cord Dorsal funiculi Spinocerebellar tracts	Upper midbrain level (6) Microscopic, special reference to spinal and trigeminal lemnisci

Quarterly schedule—Continued

PERIOD	LECTURE (1 HOUR)	LABORATORY AND DEMONSTRATION (2 OR 3 HOURS)
11	Cerebellum Gross structure Localization of function Microscopic structure Components of peduncles	Diencephalon (level 7), gross and microscopic series. Special reference to spinal and trigeminal lemnisci, lateral nucleus of thalamus, internal capsule
12	Brachium conjunctivum Medial lemniscus Lateral nucleus of thalamus Cortical areas related to deep sensibility system	Review brain-stem series, noting and inserting on sketches the structures of deep sensibility Dem. 4—Marchi and special slides on tracts of deep sensibility
13	Vestibular (equilibratory) system Inner ear, general structure Vestibular part in detail	Cerebellum. Review gross structure Dissection of peduncles Microscopic structure
14	Vestibular nerve and nuclei Vestibular tracts in the brain-stem, spinal cord, and to the cerebellum	Vestibular structures followed in brain-stem series and inserted in sketches of the proper levels already outlined
15	Auditory system Ear, microscopic structure of external and middle ear, cochlea	Cochlea, microscopic structure Dem. 5—Special slides on cerebellum and ear. Models of ear. Marchi series on vestibulospinal fasciculus
16	Cochlear nerve and nuclei Lateral lemniscus Cortical connections Reflex possibilities	Tracts and nuclei of auditory system followed in brain-stem series and inserted on outlines of proper levels already made
17	Visual system Eyeball Gross structure Microscopic structure	Eyeball Dissection of beef eye Microscopic structure, excluding the retina
18	Retina in detail	Retina and optic nerve, microscopic Dem. 6—Models and special slides on the eye and optic nerve
19	Optic nerve and chiasm Optic tract and connections Visual cortex Reflex connections	Study gross and microscopic material on upper midbrain and metathalamus and insert on sketch of level 6

Quarterly schedule—Continued

PERIOD	LECTURE (1 HOUR)	LABORATORY AND DEMONSTRATION (2 OR 3 HOURS)
20	General visceral afferent system End organs, peripheral nerves Pathways in cord and brain Gustatory system Taste buds Peripheral nerves involved Central connections	Review brain-stem series for Nn. VII., IX. and X, and Solitary fasciculus and nucleus and insert on sketches Dissection of solitary fasciculus Taste buds Microscopic structure
21	Cerebral hemispheres Weight with age, sex, etc. Significance of fissures	Study gross divisions of cerebral hemispheres on brains being dissected and on gross series
22	Cerebral localization	Review cerebral topography
23	Histology of cerebral cortex	Histology of cerebral cortex
24	Association, commissural and projection fibers	Histology of cerebral cortex Dem. 7—Histology of cerebral cortex
25	Somatic motor system Motor cortex Pyramidal system	Dissection of association bundles, lenticular nucleus, internal capsule pyramidal fibers
26	Cortico-pontile system Extrapyramidal system Corpus striatum	In gross brain series study form and relations of internal capsule and corpus striatum
27	Lower motor neurones Cranial nerves Spinal nerves Variations and double innervation in muscles Motor end plates	Study somatic motor structures in brain-stem series and spinal cord Dem. 8—Histology of corpus striatum and subthalamic region. Marchi series on pyramidal and rubrospinal tracts. Motor end plates
28	Special visceromotor system Visceral striated muscles General visceral efferent system Sympathetic ganglia	Study brain-stem series on visceral effective nuclei and nerves Complete brain-stem sketches Histology of sympathetic ganglia
29	Craniosacral division (autonomic, parasympathetic) Relation to prevertebral and terminal ganglia	Copy charts on craniosacral outflow showing course of preganglionic and postganglionic fibers to particular viscera

Quarterly schedule—Concluded

PERIOD	LECTURE (1 HOUR)	LABORATORY AND DEMONSTRATION (2 OR 3 HOURS)
30	Thoracicolumbar division (sympathetic proper) Special relation to sympathetic trunk and vertebral ganglia	Copy chart on thoracicolumbar division Dem. 9—Special slides and dissections on sympathetic ganglia, nerves, rami communicantes
31	Olfactory system Olfactory membrane, nerves, bulb, tract, central connections	Histology of olfactory membrane, and olfactory bulb Dissection of rhinencephalon
32	Ventricles of the brain Topography, significance Ependyma, chorioid plexus Cerebrospinal fluid	Dissection of brain completed Topography of the ventricles Chorioid plexus Caudate nucleus
33	Arterial supply and venous drainage of the brain	Blood supply of the brain and cord Dem. 10—Special preparations on olfactory system, ependyma, chorioid plexus and ventricles

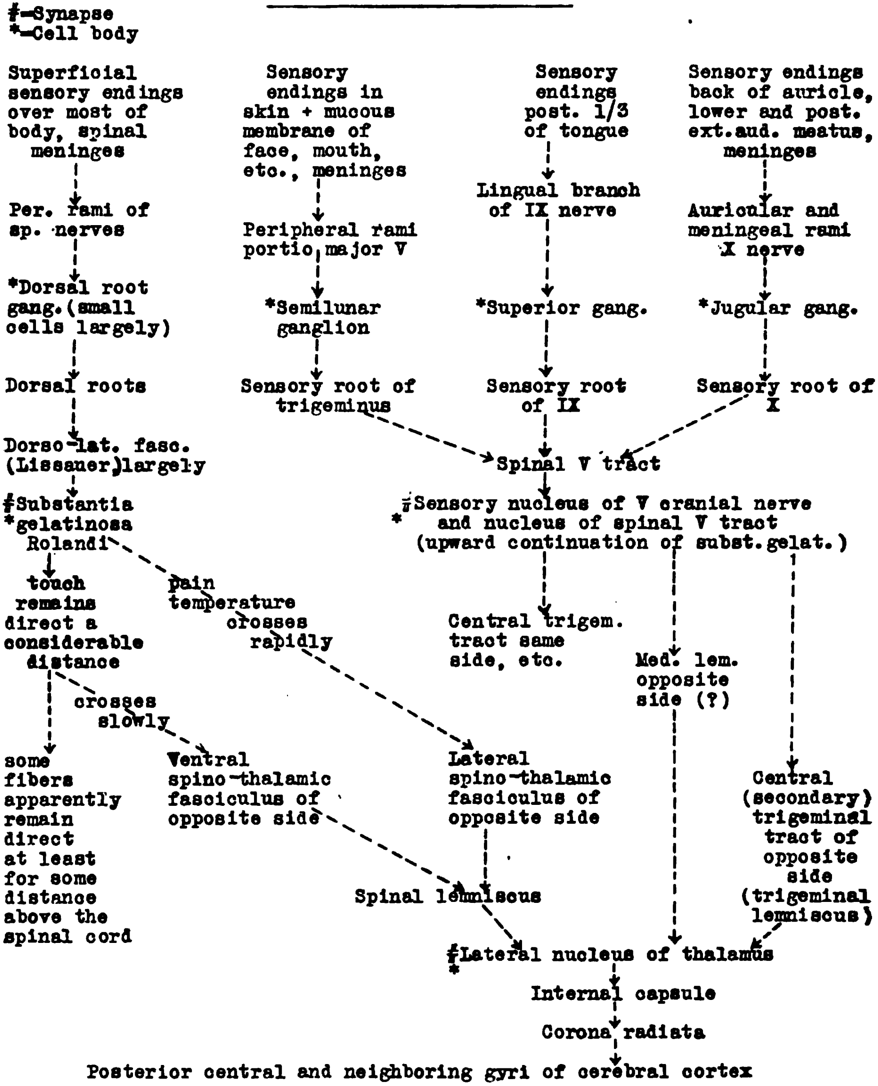
SUMMARIZING SCHEMES

In addition to large charts and models showing the position and relations of the structures by functional systems, schemes such as are shown below have been received with sufficient enthusiasm by our students to suggest that others might find them useful. They are necessarily too dogmatic and must be interpreted liberally in places where uncertainty still exists. Such points are, of course, covered in the lectures.

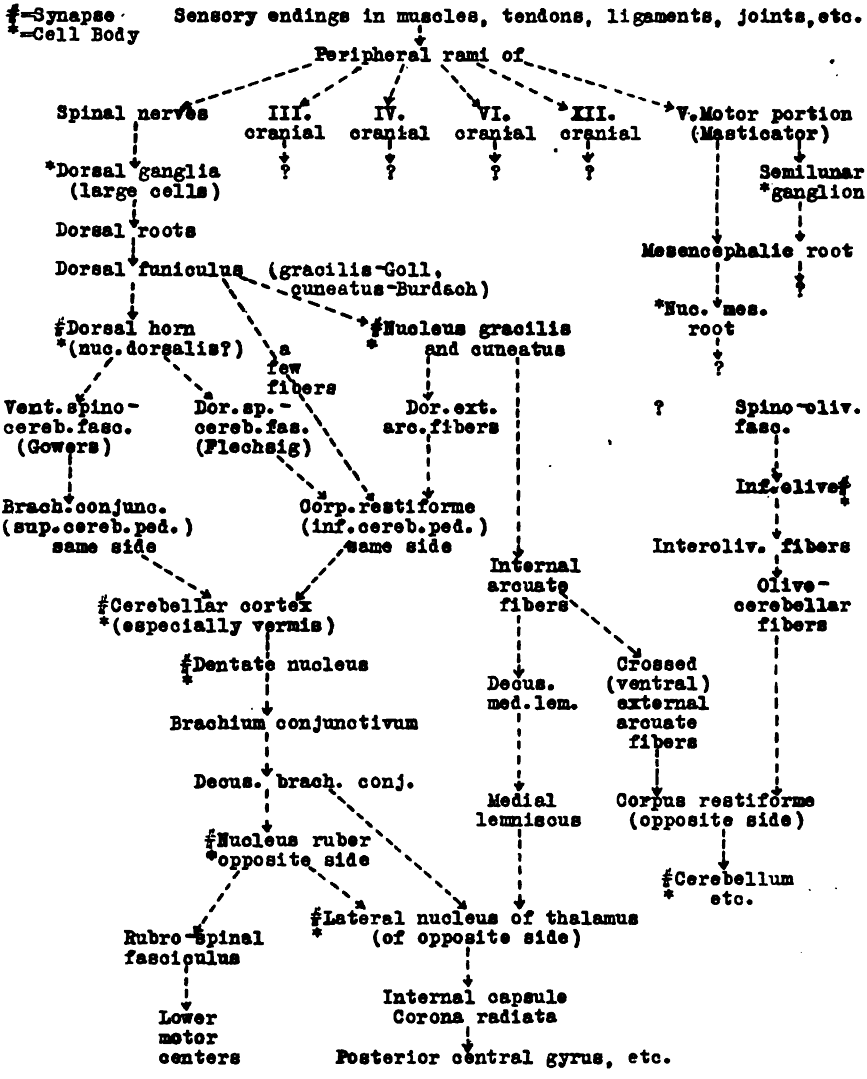
The general idea underlying the arrangement has been to make a compact and suggestive summary of each functional system. In many cases there has been sufficient space to put coordinate structures in about the same plane. The items have been so spaced and abbreviated that each system can be typewritten on an ordinary-sized stencil (size 8½ inches x 11 inches). All lines may be put in by hand or the vertical ones may be made by machine. The arrow-heads are stenciled in with a stylus shaped like a small sharp screwdriver.

It may be objected that such tabulations will be used as short-cuts and memorized at the expense of a clear idea of the position and relations within the nervous system. Students should be cautioned about this and required to pass practical examinations. On the other hand, it is a method of organizing numerous details into important units in such a fashion that it is a distinct aid to many students.

PAIN - TOUCH - TEMPERATURE

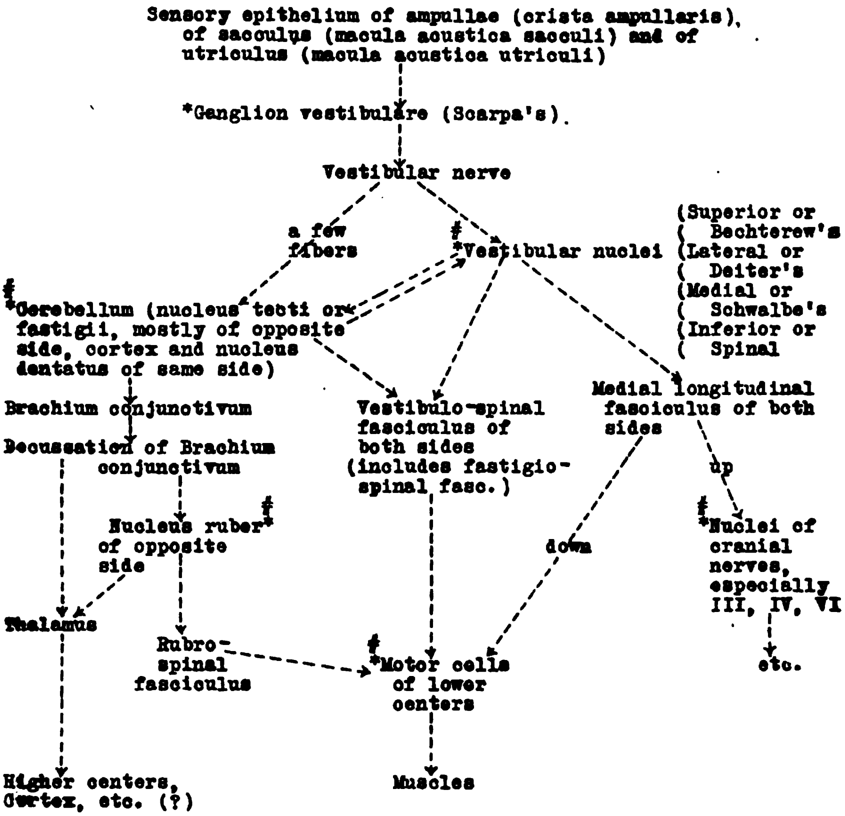

‡—Synapse
*—Cell body
Superficial sensory endings over most of body, spinal meninges
Per. rami of sp. nerves
*Dorsal root gang. (small cells largely)
Dorsal roots
Dorso-lat. fasc. (Lissauer) largely
‡Substantia *gelatinosa Rolandi
touch remains direct a considerable distance
pain temperature crosses rapidly
crosses slowly
some fibers apparently remain direct at least for some distance above the spinal cord
Ventral spino-thalamic fasciculus of opposite side
Sensory endings in skin + mucous membrane of face, mouth, etc., meninges
Peripheral rami portio major V
*Semilunar ganglion
Sensory root of trigeminus
Sensory endings post. 1/3 of tongue
Lingual branch of IX nerve
*Superior gang.
Sensory root of IX
Sensory endings back of auricle, lower and post. ext. aud. meatus, meninges
Auricular and meningeal rami X nerve
*Jugular gang.
Sensory root of X
Spinal V tract
‡*Sensory nucleus of V cranial nerve and nucleus of spinal V tract (upward continuation of subst. gelat.)
Central trigem. tract same side, etc.
Med. lem. opposite side (?)
Lateral spino-thalamic fasciculus of opposite side
Central (secondary) trigeminal tract of opposite side (trigeminal lemniscus)
Spinal lemniscus
‡*Lateral nucleus of thalamus
Internal capsule
Corona radiata
Posterior central and neighboring gyri of cerebral cortex

DEEP SENSIBILITY (Muscle Sense, Vibratory Sense, etc., Sense of Position of Members of the Body and of Passive Movement) - SPATIAL DISCRIMINATION (Two-point; Size, Shape and Texture of Surfaces; Stereognosis)


#=Synapse
*=Cell Body
Sensory endings in muscles, tendons, ligaments, joints, etc.
Peripheral rami of
Spinal nerves
III. cranial
IV. cranial
VI. cranial
XII. cranial
V. Motor portion (Masticator)
*Dorsal ganglia (large cells)
?
?
?
?
Semilunar *ganglion
Dorsal roots
Mesencephalic root
Dorsal funiculus (gracilis-Goll, cuneatus-Burdach)
*Nuc. mes. root
#Dorsal horn *(nuc. dorsalis?)
a few fibers
#Nucleus gracilis * and cuneatus
?
Vent. spino-cereb. fasc. (Gowers)
Dor. sp.-cereb. fas. (Flechsig)
Dor. ext. arc. fibers
?
Spino-oliv. fasc.
Inf. olive# *
Brach. conjunc. (sup. cereb. ped.) same side
Corp. restiforme (inf. cereb. ped.) same side
Interoliv. fibers
Internal arcuate fibers
Olivo-cerebellar fibers
#Cerebellar cortex *(especially vermis)
#Dentate nucleus *
Decus. med. lem.
Crossed (ventral) external arcuate fibers
Brachium conjunctivum
Decus. brach. conj.
Medial lemniscus
Corpus restiforme (opposite side)
#Nucleus ruber *opposite side
#Cerebellum * etc.
#Lateral nucleus of thalamus * (of opposite side)
Rubro-spinal fasciculus
Internal capsule Corona radiata
Lower motor centers
Posterior central gyrus, etc.

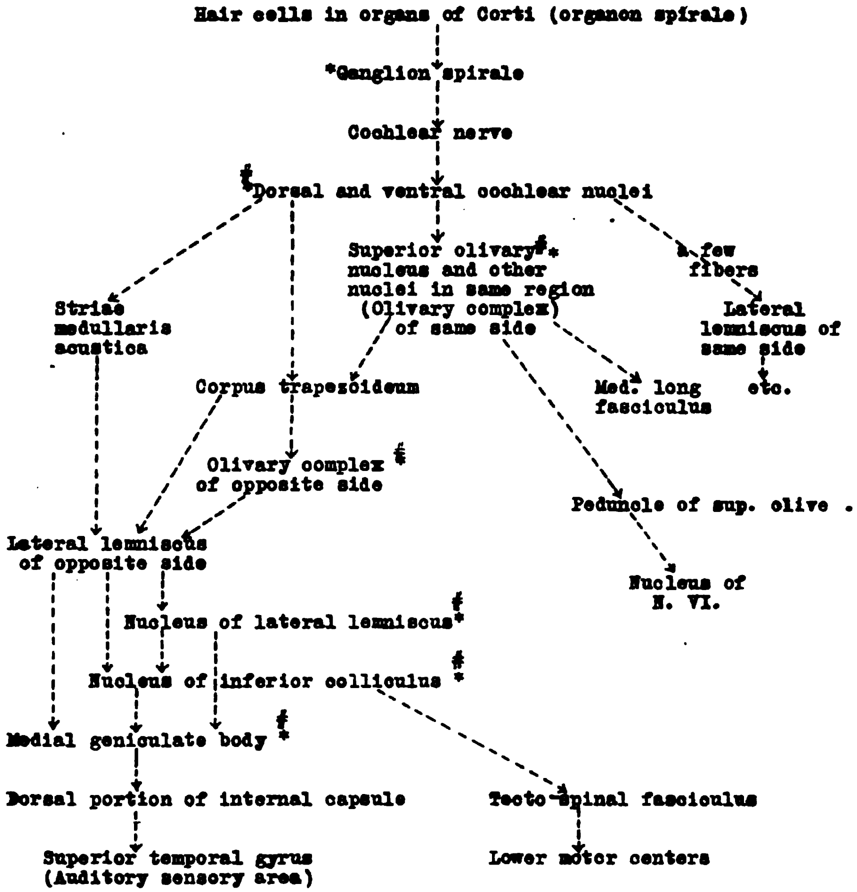
VESTIBULAR OR EQUILIBRATORY SYSTEM

#=Synapse
*=Cell body


Sensory epithelium of ampullae (crista ampullaris), of sacculus (macula acustica sacculi) and of utriculus (macula acustica utriculi)
*Ganglion vestibulare (Scarpa's).
Vestibular nerve
a few fibers
#
*Vestibular nuclei
(Superior or
(Bechterew's
(Lateral or
(Deiter's
(Medial or
(Schwalbe's
(Inferior or
(Spinal
#
*Cerebellum (nucleus tecti or fastigii, mostly of opposite side, cortex and nucleus dentatus of same side)
Brachium conjunctivum
Decussation of Brachium conjunctivum
#
Nucleus ruber* of opposite side
Thalamus
Higher centers, Cortex, etc. (?)
Rubro-spinal fasciculus
Vestibulo-spinal fasciculus of both sides (includes fastigio-spinal fasc.)
#
*Motor cells of lower centers
Muscles
Medial longitudinal fasciculus of both sides
up
down
#
*Nuclei of cranial nerves, especially III, IV, VI
etc.

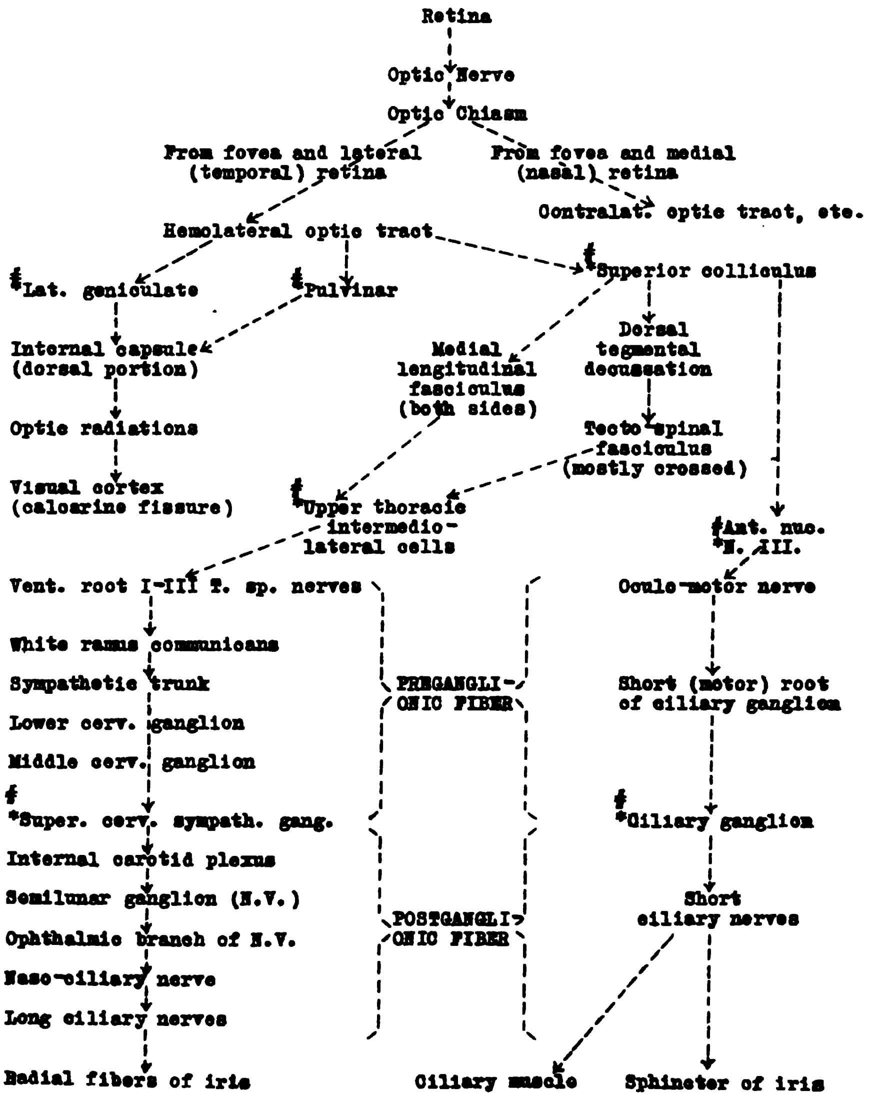
#-Synapse
*-Cell body

AUDITORY SYSTEM

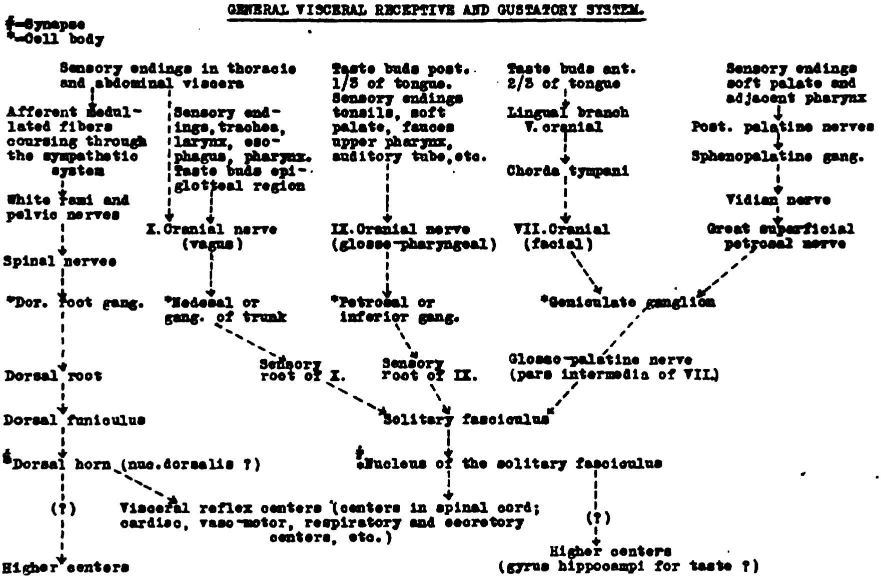

Hair cells in organs of Corti (organon spirale)
*Ganglion spirale
Cochlear nerve
#*Dorsal and ventral cochlear nuclei
Striae medullaris acustica
Superior olivary#* nucleus and other nuclei in same region (Olivary complex) of same side
A few fibers
Lateral lemniscus of same side
Corpus trapezoideum
Med. long fasciculus
etc.
Olivary complex # of opposite side
Peduncle of sup. olive
Lateral lemniscus of opposite side
Nucleus of N. VI.
Nucleus of lateral lemniscus #*
Nucleus of inferior colliculus #*
Medial geniculate body #*
Dorsal portion of internal capsule
Tecto-spinal fasciculus
Superior temporal gyrus (Auditory sensory area)
Lower motor centers

*—Cell Body.
#—Synapse.

VISUAL SYSTEM


Retina
Optic Nerve
Optic Chiasm
From fovea and lateral (temporal) retina
From fovea and medial (nasal) retina
Contralat. optic tract, etc.
Homolateral optic tract
#*Lat. geniculate
#Pulvinar
#*Superior colliculus
Internal capsule (dorsal portion)
Medial longitudinal fasciculus (both sides)
Dorsal tegmental decussation
Optic radiations
Tecto-spinal fasciculus (mostly crossed)
Visual cortex (calcarine fissure)
#*Upper thoracic intermedio-lateral cells
#Ant. nuc. *N. III.
Vent. root I-III T. sp. nerves
Oculo-motor nerve
White ramus communicans
Sympathetic trunk
PREGANGLIONIC FIBER
Short (motor) root of ciliary ganglion
Lower cerv. ganglion
Middle cerv. ganglion
#*Super. cerv. sympath. gang.
#*Ciliary ganglion
Internal carotid plexus
Semilunar ganglion (N.V.)
Short ciliary nerves
POSTGANGLIONIC FIBER
Ophthalmic branch of N.V.
Naso-ciliary nerve
Long ciliary nerves
Radial fibers of iris
Ciliary muscle
Sphincter of iris

GENERAL VISCERAL RECEPTIVE AND GUSTATORY SYSTEM.


‡=Synapse
*=Cell body
Sensory endings in thoracic and abdominal viscera
Afferent medullated fibers coursing through the sympathetic system
White rami and pelvic nerves
Spinal nerves
*Dor. root gang.
Dorsal root
Dorsal funiculus
‡Dorsal horn (nuc.dorsalis ?)
(?)
Higher centers
Sensory endings, trachea, larynx, esophagus, pharynx. Taste buds epiglottal region
X.Cranial nerve (vagus)
*Nodosal or gang. of trunk
Sensory root of X.
Taste buds post. 1/3 of tongue. Sensory endings tonsils, soft palate, fauces upper pharynx, auditory tube, etc.
IX.Cranial nerve (glosso-pharyngeal)
*Petrosal or inferior gang.
Sensory root of IX.
Taste buds ant. 2/3 of tongue
Lingual branch V. cranial
Chorda tympani
VII.Cranial (facial)
Sensory endings soft palate and adjacent pharynx
Post. palatine nerves
Sphenopalatine gang.
Vidian nerve
Great superficial petrosal nerve
*Geniculate ganglion
Glosso-palatine nerve (pars intermedia of VII.)
Solitary fasciculus
‡Nucleus of the solitary fasciculus
Visceral reflex centers (centers in spinal cord; cardiac, vaso-motor, respiratory and secretory centers, etc.)
(?)
Higher centers (gyrus hippocampi for taste ?)

CHANGES IN THE MAMMARY GLAND OF THE ALBINO RAT (MUS NORVEGICUS ALBINUS) DURING THE SECOND HALF OF PREGNANCY*

FRANK L. ROBERTS

The primary purpose of the present study is to determine the changes which occur in the mammary gland of the albino rat during pregnancy, and thereby to establish for this animal a norm which would serve as a basis for experimental work. The subject is old, and much has been written concerning it. But a survey of the literature will show that there has been very little detailed work on the gland during pregnancy on any one animal form, with the exception of Schil's work on the rabbit. Hence it was thought desirable to investigate the subject in the rat, supplementing the researches of Myers, who had worked out the earlier stages of the development of the mammary gland in this animal.

The material comprises the glands of eleven pregnant albino rats (*Mus norvegicus albinus*), primiparae, and two virgin cats; all from the colony in the Institute of Anatomy. The material represents stages from the thirteenth day of pregnancy to within a few hours of delivery and includes the following six stages: thirteen days; sixteen days and twelve hours; eighteen days and twelve hours; nineteen days; twenty days; and twenty days and nine hours. Material for the earlier stages of pregnancy was not available.

The technic of removal and preparation of the glands has been described by Myers[22] which briefly is as follows: The animals were killed with ether; the skin with all the mammary glands was removed immediately and pinned out on a sheet of cork, hairy surface down, and placed in Zenker's fluid.

Cleared preparations were made in the manner described by Myers[22] which is essentially the method Lane-Claypon and Starling used in work on the rabbit. These preparations were mounted in xylol-gum-damar in shallow glass cells.

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* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Arts, 1919.

In preparing material for microscopic sections, portions of the fixed gland were removed carefully and imbedded in hard paraffin. In sectioning the nipples it was found almost impossible to cut the tough skin when it was imbedded in ordinary paraffin. Therefore Johnston's asphalt method (Guyer), as modified, I believe, by Dr. J. T. Patterson, was employed. Crude rubber was cut into very fine bits with a pair of sharp curved scissors. About three teaspoonfuls of this finely divided rubber were put into a pint of paraffin, melting point 65°C. The mixture was left in the oven for three days and frequently stirred, and by the end of three days most of the rubber had passed into solution; it was then removed from the oven and cooled. A part was melted only when needed for imbedding, since it was soon ascertained that if the mixture is kept melted for much more than three days, the rubber tends to precipitate. This treatment toughens the paraffin to such a degree that the skin imbedded in it can easily be cut.

Sections of the mammary gland and nipple were cut at 3, 4, 5, 7 and 10 microns in thickness. Some sections were stained with Mallory's connective tissue stain; some with Weigert's iron hæmatoxylin, counter-stained with Van Gieson's stain; and some with a 1 per cent aqueous solution of cresyl violet. Another series were stained with Unna's orcein for elastic tissue. A few fresh frozen sections were stained with osmic acid and Sudan III, in order to show the distribution of fat.

The Sudan III stain deserves particular mention because of the beautiful results obtained and because of some of the difficulties encountered in using it. Paraffin sections were passed in the usual way from xylol to water, and from water were placed in the stain for twenty minutes. From the stain the sections, after rinsing well in water, were plunged directly into 95 per cent alcohol for a few seconds; then for the same length of time into absolute alcohol; then into a mixture of absolute and xylol a few seconds; and finally into xylol for three minutes. They were finally mounted in toluol-gum-damar.

The reason for the short treatment with the alcohol and xylol is because it was observed that for some reason the alcohols and xylol quickly decolorize the sections to such a degree that there is no longer any differentiation of the tissue elements.

Cresyl violet, as is well known, gives a most excellent differentiation to the mast cells, sharply marks off the glandular from the connective tissue, and gives very good cytological details.

In studying the increase in the size of the nuclei, cells, and alveoli, a Leitz ocular micrometer was used with a Spencer's mechanical stage. The nuclei measured were those which showed most clearly the nucleolus. The alveoli measured were those in which the lumen was most clearly outlined and nearly circular. The entire alveolus was measured from the base of one cell to the base of the opposite cell. The lumina were measured in their transverse diameters, and the epithelial cells were measured along the diameter perpendicular to the circumference of the alveolus. There was no attempt at extremely accurate measurements as the only thing desired was to determine roughly the change in the size of the alveoli and cells from the thirteenth to the twentieth day.

A few measurements were taken by calipers on the nipples of the pregnant animals and served merely to confirm what could easily be seen with the naked eye, namely, that there is a marked increase in the size of the nipple during pregnancy.

GROSS CHANGES IN THE MAMMARY GLAND DURING PREGNANCY

The only gross change that can be observed externally in the gland of the living animal during pregnancy is the increase in the size of the nipples. If a pregnant rat is suspended by the head or tail the nipples are seen to be very prominent. Part of this prominence is due of course to the stretching of the abdominal skin, but by far the most of it is due to an actual increase in the size of the nipples. This increase in size is apparent to the naked eye and was easily verified by a few rough measurements with the calipers on virgin and pregnant animals.

The increase in the length of the nipple during pregnancy is associated with the complete degeneration of the 'epithelial hood' which surrounds, at least in part, the virgin nipple. Myers[24] has described a partial degeneration of this hood at the time of puberty, but in virgin rats even four months old this hood has not entirely disappeared and is only partly degenerated on one side. During pregnancy, however, the degeneration is completed. At the end of pregnancy there is not a remnant of this hood left, except some necrotic debris in the groove which has taken its place (Fig. 98).

The nipple, accordingly, in pregnant and lactating rats may easily be drawn out to nearly double its apparent length. In fact it is drawn out during the act of suckling, and the purpose of the degeneration of the epithelial hood is doubtless to allow for this increase in the length of the nipple for the accommodation of the young.

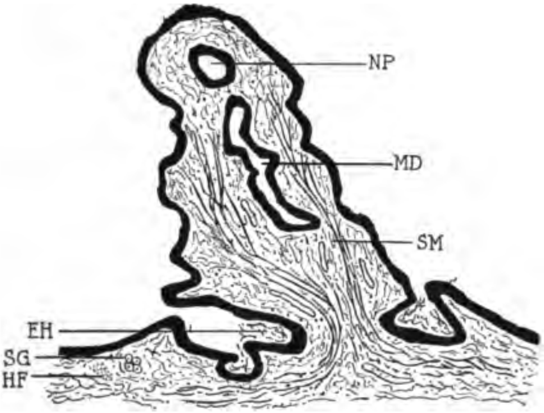

FIG. 98.—Drawing of nipple. Rat sixteen days and twelve hours pregnant. The epithelial hood has entirely disappeared, leaving a groove, *E.H.*, in its place. This groove contains some granular débris, *D.* Well developed smooth muscle, *S.M.*, about the main duct, *M.D.*, of the nipple. The smooth muscle does not extend up to the nipple pore, *N.P.* A hair follicle, *H.F.*, and a sebaceous gland, *S.G.*, are shown on the left. Zenker's fixation, Weigert's iron hematoxylin counterstained with Van Gieson's stain; 7 microns. This section should be compared with Figure 14 in Myers' paper, which shows only a slight degeneration of the hood.

Upon removing the skin from the freshly killed animal, the mammary glands are seen as whitish masses raised slightly above the surface of the rest of the skin. The glands are streaked with numerous blood vessels, which indicate the extremely rich blood supply which the glands have during gestation. The arrangement of the individual glands is best made out with the aid of the cleared preparations.

In the cleared specimens it can be seen that there has been a tremendous increase in the amount of the glandular tissue, which, roughly, forms two horseshoe-shaped masses, anterior and posterior, with their concavities facing each other. This appearance is brought about as follows: There is an overlapping of the glandular tissue of the abdominal and inguinal glands of the same side. The second inguinals of either side overlap across the mid-ventral line of the body and thus the caudal C-shaped mass of glandular tissue is formed.

Likewise there is an overlapping of the three thoracic glands of the same side, and a transverse overlapping of the glandular tissue of the first thoracic glands of opposite sides. There is no overlapping of the last thoracic and abdominal glands, and no transverse overlapping anywhere except in the two regions noted above.

Myers [22] has called attention to this arrangement of the glandular tissue in the virgin animal and the overlapping is merely emphasized by the tremendous proliferation of the glands during pregnancy.

A closer study of the cleared preparations shows that there is one main duct leading to the nipple pore and all the rest of the ducts branch off from this one, as shown by Meyers [22,25]. From the sub-branches of the secondary ducts the buds are seen which in the thirteen-day stage are nearly spherical while they are larger and roughly ellipsoidal in the twenty-day stage.

These bud-like outgrowths on section are seen to consist each of a group of alveoli. Thus each bud represents a lobule, while a secondary duct with its lobules constitutes a lobe. However, it should be noted that the excretory duct of each lobe opens into the main duct before the main duct passes through the substance of the nipple.

Although (as will be shown later) practically no mitoses or amitoses appear in the gland during this period, the cleared preparation in the gland parenchyma of the twenty day stage showed more lobules than that of the thirteen day stage. It is very probable, however, that this represents an individual variation rather than a multiplication of elements in the second part of pregnancy. Some individual variation in the size and arrangement of the mammary glands of the albino rat is always to be expected. This was clearly shown by Myers [22], who was working on rats from the same colony from which the material for this study was taken.

Further evidence that this apparent increase in the number of lobules is due to individual variation is that there is no visible difference in the number of lobules in the glands of the thirteen day stage and those of the sixteen day and the eighteen day stages. The cleared preparation of the nineteen day stage was lost and hence was not available for a comparison, but it is very improbable that a multiplication of the elements would not begin before the nineteenth day of pregnancy. If there were an increase in the number of lobules of the mammary gland in the latter part of pregnancy we would expect to find some evidence of the increase in the time elapsing from the thirteenth day to the nineteenth day stage.

It might be objected that this lack of difference in the stages studied represents an individual variation while the increased number of lobules represent the true condition. In the absence of evidence of cell division, however, I believe it safe to conclude from the material thus far studied that there is probably no increase in the number of glandular elements in the second period of pregnancy, from the thirteenth day onward.

CHANGES IN MICROSCOPIC STRUCTURE

1. *The nipple.*—Aside from the increase in the size of the nipple and the disappearance of the epithelial hood, the main difference in the structure of the nipples of pregnant and virgin animals is in the amount of smooth muscle around the main duct. This smooth muscle, described by Myers [23] in virgin animals, is well developed by the end of pregnancy. Since it is attached externally to the processes of the epithelium which project into the corium of the nipple and internally is continuous with the smooth muscle layer directly under the skin, it is probable that the purpose of this muscle is to aid the elastic tissue in retracting the nipple after it has been drawn out in the act of suckling (Fig. 98). It also may aid in compressing the main duct of the nipple and thus facilitate the flow of milk; but I believe this is rather the minor rôle of this muscle. The emptying of the ducts appears to be rather a passive process, and it seems unnecessary to assume that there must be some muscular elements, as, for example, the myoepithelial cells of La Croix and others, to aid in expelling the secretion.

The lumen of the main duct of the nipple is enlarged considerably during pregnancy. This enlargement is purely mechanical and is due to the increase in the amount of secretion in the duct as pregnancy advances. There is apparently no change in the epithelium of the duct from that in virgin animals, which was accurately described by Myers [24].

2. *General structure.*—A low power view of a section of the thoracic mammary gland of a thirteen day pregnant rat gives a picture which, excluding the panniculus carnosus, represents in general the picture of any one of the mammary glands at any stage of pregnancy. The picture differs from that of a section of a virgin gland in the presence

of lobules, more ducts, more blood vessels, and more cellular elements in the stroma.

A relatively broad band of striated muscle, the panniculus carnosus, is seen running through the center of the section. On either side of this muscle is arranged the glandular parenchyma in the form of lobules and ducts scattered through the fatty tissue. Only occasionally a duct opening directly into a lobule is seen, an appearance which is brought about by the arrangement of ducts and lobules. It is to be remembered that the lobules bud off irregularly from the duct and hence in many places the duct will be cut and not the lobule; in other places the lobule will be apparently isolated, and only when the section happens to cut the narrow stalk connecting the lobule and duct will the true arrangement be seen.

Blood vessels and nerves are scattered throughout the sections. The large nerves lie in close proximity to the muscle, which they supply. The ducts and lobules are surrounded by sheaths of fibrous connective tissue and the rest of the stroma is mostly adipose. In fact the whole picture, excluding the muscle, gives an impression of small islands of glandular tissue in a lake of fat (Fig. 99).

This distribution of the adipose tissue is interesting from the point of view of the development of the mammary gland. Myers has shown that in young albino rats the fat is soon laid down in certain definite regions and into these regional pads of fat the mammary gland pushes its way. Hence we see the explanation for the large amount of adipose tissue in sections of the pregnant gland.

In discussing the finer structure of the gland the following structures will be described in turn: (3) changes in the stroma; (4) changes in the ducts; and (5) changes in the acini.

3. *Changes in the stroma.*—Any stage from the thirteenth to the twentieth day might be described with reference to the stroma and the resulting picture with a few minor changes would represent the stroma of any of the other stages. That is, the stroma is the more constant element in the gland, while the parenchyma is undergoing radical changes.

Each duct is surrounded by a dense sheath of connective tissue, which is prolonged around the lobules which are drained by this duct (Fig. 100). From the lobular sheath, prolongations extend inwards and surround the individual alveoli. Where the sheath leaves the duct to pass around the lobule, it suddenly becomes very much thinner, an arrangement which is easily understood if we refer to Wahl's description of the mode of proliferation of the ducts and lobules.

Here an explanation is given for the appearance of the stroma of the gland after all the lobules and acini are formed. The first bud which pushes out carries with it a covering of fibrous connective tissue derived from the sheath of the parent duct. This bud, enlarging, keeps pushing ahead of it the connective tissue sheath, which as a result becomes very much thinned. Of course this thinning out would not result if the growth of the stroma of the gland kept pace with that of the parenchyma; but Duclert and Steinhaus have clearly shown that the stroma lags far behind the parenchyma as regards growth. None of the specimens studied showed any structure resembling a membrana propria.

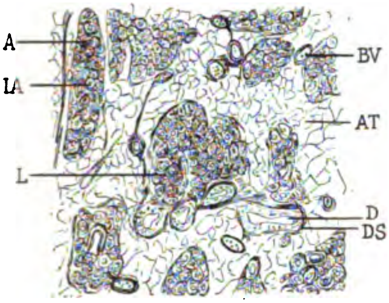

FIG. 99.

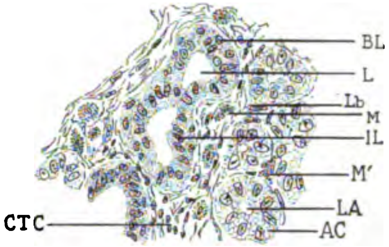

FIG. 100.

FIG. 99.—Drawing (low power) of a section of one of the abdominal mammary glands of a rat eighteen days and twelve hours pregnant. Panniculus carnosus muscle not shown. *BV*, blood vessel; *AT*, adipose tissue; *D*, duct; *DS*, duct sheath; *L*, lobule; *IA*, interalveolar connective tissue; *A*, alveolus. Zenker's fixation; Mallory's connective tissue stain; 5 microns.

FIG. 100.—Section through duct and neighboring acini. Rat fifteen days pregnant. Mast cells and the rapid thinning of the fibrous sheath of the duct are shown, as this sheath passes around the lobule at *LB*. *BL*, basal layer of duct epithelium; *L*, lumen of duct; *M*, mast cell; *M'*, mast cell between two alveoli; *IL*, inner layer of duct epithelium. No vacuolization shown at this stage. *LA*, lumen of alveolus; *AC*, vacuolated alveolar cytoplasm; *CTC*, cellular elements of connective tissue. Zenker's fixation; Cresyl violet stain; 4 microns.

Turning from the covering of the ducts and lobules to the covering of the individual acini, one sees that in the thirteen day stage it is relatively loose (Fig. 101), being composed of elastic and collagenous fibers and traversed by capillaries. By the end of pregnancy, however, the acini have enlarged to such an extent that this sheath has been stretched. As a result it appears more dense and is closely applied to the base of the alveolar epithelium, giving an appearance of a membrana propria.

That this appearance of a membrana propria is a result of the stretching of the interlobular connective tissue and that the membrana propria, as such, does not exist in the mammary gland of the pregnant albino rat, is shown by a study of the stages used for this work. Figure 101 shows that the sheath is loose and only when the acini are distended with secretion do we get the appearance of a basement membrane (Fig. 102). Since the sheaths of the ducts are imbedded in soft adipose tissue, no distention of the ducts stretches the sheath since the adipose tissue yields to the pressure. Hence there is no appearance of any structure resembling a membrana propria around the ducts.

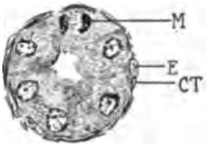

Fig. 101.

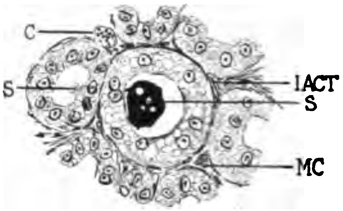

Fig. 102.

Fig. 101.—Alveolus from gland of rat thirteen days pregnant. Connective tissue sheath, *CT*, is relatively loose. Endothelial cell nuclei, *E*, show no pressure effects. Mitotic figure, *M*, shown in one of the cells. Zenker's fixation. Weigert's iron-hematoxylin, counterstained with Van Gieson's stain; 4 microns.

Fig. 102.—Acini from gland of rat, eighteen days and twelve hours pregnant. *IACT*, interalveolar connective tissue is seen to be stretched around the acinus, giving an appearance of a membrana propria. A mass of secretion, *S*, is seen in the lumen of the central acinus. Secretion granules, *S*, are seen being extruded from one of the acinar cells. A distended capillary, *C*, and a mast cell, *MC*, are also shown. Zenker's fixation; Cresyl violet stain; 4 microns.

Besides the prolongations about the lobules, the sheath about the ducts send out projections which become continuous with the sheaths around the blood vessels of this region and everywhere are continuous with the fibrous framework of the adipose tissue (Fig. 99). Where a duct lies next to a muscle, as in the thoracic glands, the sheath around the duct is continuous with the perimysium of the muscle. In the region of the nipple, the ducts merely pass through the subcutaneous tissue and lose the well-defined sheaths which they possess deeper in the gland.

A close study of the sheaths around the ducts, lobules, and acini reveals many elastic fibers in these sheaths. Several authors have attempted to point out a connection between pregnancy and the amount of elastic tissue in the stroma of the mammary gland. As shown in the review of the literature, little has been accomplished towards a solution of the problem. In my material there is an unfortunate arrangement of the age of the specimens. With two exceptions the further advanced the pregnancy the older was the rat. As a result all I can do is to describe the elastic tissue as I found it and to point out some factors suggested by the findings.

In sections stained with Unna's orcein, the elastic tissue fibers are seen to be running lengthwise in the connective tissue sheaths around the ducts, and are prolonged in the form of a few fine fibers around each lobule. From this lobular sheath fine fibrils are sent in which, in the latter stages of pregnancy, surround each alveolus.

In the thirteen day stage, in most cases it is extremely hard to see any elastic tissue round the individual alveoli, but by the end of eighteen days and twelve hours it is easily seen that each alveolus is completely surrounded by a fine network of elastic tissue.

In the earlier stages the elastic fibers are fine and delicate, while in the later stages most of them are exceedingly coarse. The sections show that in the specimens used for this study there is apparently a great increase in the amount of elastic tissue around the ducts from the thirteenth to the twentieth day. This increase is progressive; that is, the fifteenth day stage has more than the thirteen, the eighteen more than the fifteen day stage, and so on.

On the face of it, this would indicate that pregnancy causes a proliferation of elastic tissue in the mammary gland, but as previously pointed out, the age of these specimens, with two exceptions, is arranged parallel with the advance of pregnancy. The representative stages are arranged in the order that the amount of elastic tissue increases and the age of each specimen is indicated:

1. Rat 102, 5½ months, 13 days pregnant
2. Rat 106, 6 months, 15 days pregnant
3. Rat 105, 10 months, 16 days, 12 hours pregnant
4. Rat 101, 3½ months, 18 days, 12 hours pregnant
5. Rat 104, 10 months, 19 days pregnant
6. Rat 103, 9 months, 20 days, 9 hours pregnant
7. Rat 110a, 3½ months, 20 days pregnant.

Between Rats 1 and 2 it was sometimes difficult to determine which had the more elastic tissue, and this was also the case with Rats 5 and

6, but with Rats 1 and 4 there was no question. Rat 4 had much more elastic tissue than did Rat 1, although the former was two months younger than the latter. Rat 110a had much more elastic tissue than Rat 105, and very much more than a virgin rat 12 months old (Figs. 103 and 104).

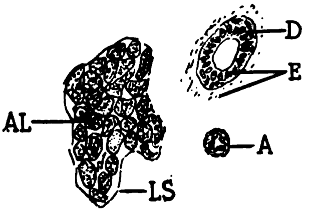

FIG. 103.

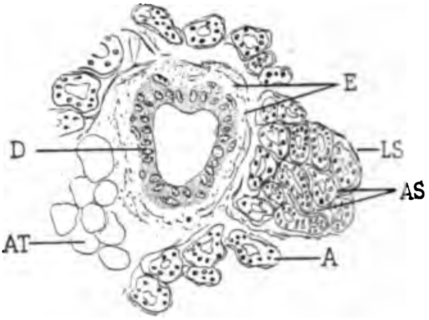

FIG. 104.

FIG. 103.—Sketch showing elastic fibers, *E*, around a duct, *D*. A well defined elastic sheath, *LS*, is seen about the lobule. The alveoli, *AL*, show almost no elastic tissue around them. An arteriole is seen at *A*. Section from gland of a rat five and one-half months old, thirteen days pregnant. Zenker's fixation; Unna's orcein stain; 4 microns.

FIG. 104.—Compare this section with the section in Figure 103. Here there are a great many more elastic fibers, *E*, about the duct, *D*. The lobular sheath, *LS*, is well defined and the acinar elastic sheaths, *AS*, have appeared. An alveolus is labeled at *A*. *AT* is adipose tissue. Section from rat three and one-half months old; eighteen days and twelve hours pregnant. Zenker's fixation; Unna's orcein stain; 4 microns.

With regard to the interalveolar elastic tissue, therefore, one pertinent fact stands out. The alveoli are new formations which appear after the beginning of pregnancy, and hence age can play no direct part in their formation. But during pregnancy, the further advanced the pregnancy, the more prominent do the interalveolar elastic tissue fibers become. The picture thus presented suggests very strongly that pregnancy stimulates the proliferation of elastic tissue in the mammary gland of the albino rat (Bierich).

The adipose tissue was very plentiful in the stroma of the gland in all stages studied, and its distribution and significance have already been referred to under the general structure of the gland.

The stroma of the mammary gland is very rich in cellular elements, many of which are of the wandering type. A great number of these wandering cells are mast cells, which are scattered throughout the stroma, in the connective tissue sheaths around the ducts, in the walls of blood vessels, in the meshes of the adipose tissue, and between the alveoli. It should be noted here that mast cells are not only common in the mammary gland of the albino rat during pregnancy but, according to Downey, are present in large numbers in this animal during its whole life. They are found most plentifully in the subcutaneous tissues, but are also found free in the peritoneal fluid and in the lymph nodes.

Many other wandering cells of leukocytic or lymphocytic type were found in the stroma in all the stages studied. In many cases in which these cells were found between the alveoli it was difficult to decide whether they were inside or outside the capillaries.

Scattered throughout the stroma, but tending for the most part to be located in close proximity to the lobules are many arterioles which send capillary branches in to supply the lobules. These intralobular, or more accurately, interalveolar capillaries are very thin walled and in most places are represented only by endothelial cells. In the thirteen day stage, these capillaries show no distention and the nuclei of the endothelial cells are large and vesicular, showing no evidence of being subjected to pressure. In the sixteen day and twelve hour stage, however, these capillaries are beginning to dilate, and the endothelial nuclei are flatter as a result of the increased pressure from the expanding alveolus. In the eighteen day and twelve hour stage and in the nineteen day stage, the capillaries are greatly dilated. At twenty days and nine hours (a few hours before delivery), they are enormously distended with red blood corpuscles, and the endothelial nuclei are very much flattened.

In regions where striated muscle is seen, large nerve trunks also appear lying in close proximity to the muscle. They are probably destined for the most part to the supply of these muscles. No attempt was made in this investigation to study the nerve supply to the gland substance.

4. *Changes in the ducts.*—The epithelium lining the ducts in the mammary gland of the white rat is double-layered throughout. The inner cells are cylindrical or cuboidal, regularly arranged, with their long axes perpendicular to the axis of the duct.

The cells making up the deep or peripheral layer of the duct epithelium are smaller and more irregularly arranged. They are irregularly flattened cuboidal and are arranged with their short axis parallel with the long axis of the inner layer of cells, that is, they tend to encircle the duct (Fig. 105). In many places these cells appear to send processes up for a short distance between the cells making up the inner layer.

In the thirteen day stage, the cytoplasm of the inner layer of duct cells is finely granular, almost homogeneous, and shows no sign of secretory activity. This condition holds true until the sixteen day and twelve hour stage. In this stage a few fine vacuoles can be seen in the cytoplasm of the inner layer of cells. These vacuoles are not numerous but tend to show that secretory activity on the part of these cells has begun.

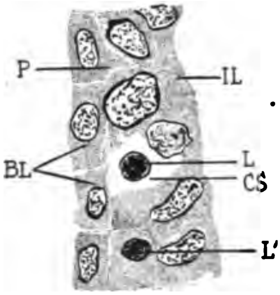

Fig. 105.

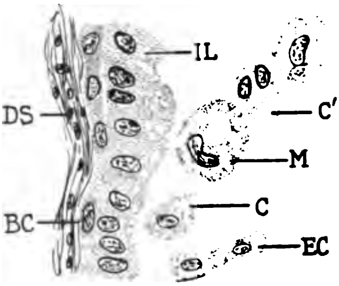

Fig. 106.

Fig. 105.—Section through the wall of a duct of a gland of a rat thirteen days pregnant. The basal layer of cells, *BL*, are shown with a process, *P*, sent up between the cells of the inner layer, *IL*. This section also shows a lymphocyte (?), *L*, in the wall of the duct and surrounded by a clear space, *CS*. Another suspected nucleus is shown at *L′*. Zenker's fixation; Cresyl violet stain; 5 microns.

Fig. 106.—Portion of the wall of a duct and colostrum corpuscles in the lumen from the gland of a rat nineteen days pregnant. *IL*, inner layer of cells showing secretory activity of cytoplasm; *BC*, basal cell. No vacuoles are present in any of the basal cells. *DS*, duct sheath; *C*. colostrum corpuscle with nucleus identical with those of the inner layer of epithelial cells of the ducts; *C′*, colostrum corpuscle with double or fragmented nucleus; *M*, colostrum corpuscle which resembles fatty macrophage. Note crescent shaped nucleus and abundant cytoplasm. *EC*, desquamated epithelial cells still adherent to each other, seemingly end to end. Zenker's fixation; Cresyl violet stain; 6 microns. × 750.

From sixteen days and twelve hours up to within a few hours of delivery the vacuolization of the cytoplasm of the inner layer of epithelial cells becomes progressively more and more pronounced and at the end of pregnancy these cells appear to be actively secreting milk (Fig. 106).

The cytoplasm of the peripheral layer of duct cells is finely granular and almost homogeneous, and even in the last stages of pregnancy these cells show no sign of secretory activity.

In the thirteen and the fifteen day stages, the nuclei of the inner layer of cells are in many places elliptical and in others round. They occupy about the middle of the cell. They are for the most part so crowded that as a consequence there seems to be very little cytoplasm at the sides of the nuclei and the line of demarcation between the individual cells is extremely poorly defined. The chromatin is scattered in the form of granules, more or less uniformly throughout the nucleus, but is not plentiful enough to make the structure look dark. The nuclei are rather vesicular in appearance, but not so much so as the nuclei of the acini, which will be described later. The explanation for the fact that in some places the nuclei appear elliptical and in other places round may be that most of them are actually ellipsoidal, but appear round only when cut transversely to their long axis. After secretory activity begins in the cells of the inner layer, the nuclei of these cells appear to be more rounded and there is more cytoplasm between the individual nuclei.

The nuclei of the deep layer of cells are round, relatively small, and are placed in each case near the center of the cell.

It is these basal cells that have probably been mistaken by many authors (Benda, Berka[3], La Croix and others) for myoepithelial cells. Their shape and the fact that they send up small processes between the cells above them suggest the myoepithelial cells of the sweat glands. Their staining reactions and general appearance however, in the ducts of the mammary gland of the albino rat, indicate that they are merely a basal layer of irregularly shaped and arranged epithelial cells. Some of the more common differential stains (Mallory's connective tissue stain, Van Gieson's stain, and cresyl violet) were used on these preparations, and all of them show conclusively that these cells are epithelial in structure. Whether or not they possess contractile properties I am unable to state, but as mentioned under the discussion on the smooth muscle in the nipple, there seems to be no reason for assuming that these cells must have contractile properties in order to aid in emptying the milk ducts.

5. *Changes in the acini.*—The changes in the acini will be discussed in the following order: (a) changes in the size of the alveoli, cells, and lumina; (b) cytoplasmic changes including secretion; and (c) nuclear changes.

The alveoli, in all stages, are lined with a single layer of columnar or cuboidal cells, which are arranged around a central lumen. The lumina of the alveoli increase in size during the latter half of pregnancy, from an average of 5.8 microns in the thirteen day stage to

17.5 microns in the twenty day and nine hour stage. This increase progresses as follows: thirteen days, 5.8 microns; fifteen days, 7.2 microns; sixteen days and twelve hours, 8.0 microns; eighteen days and twelve hours, 19.1 microns; nineteen days, 13.7 microns; and twenty days and nine hours, 17.5 microns.

While these changes were going on in the lumen of the alveoli, the average diameter of the alveoli was increasing as follows: thirteen days, 30.8 microns; fifteen days, 31.0 microns; sixteen days and twelve hours, 32.0 microns; eighteen days and twelve hours, 35.9 microns; nineteen days, 36.8 microns; and twenty days and nine hours, 40.6 microns.

In the same stages, the average height of the epithelial cells was as follows: thirteen days, 11.1 microns; fifteen days, 10.7 microns; sixteen days and twelve hours, 9.3 microns; eighteen days and twelve hours, 8.5 microns; nineteen days, 11.7 microns; and twenty days and nine hours, 12.1 microns.

The foregoing figures represent an average of twenty measurements for each stage. They are only approximate, of course, as the relatively few observations cannot be expected to give more than a rough index of the changes in the successive stages. However, the figures indicate that there has been a marked increase in the size of the lumina of the alveoli, and that there has been an increase in the total diameter of the alveolus, while the alveolar cells have undergone but little change in height.

The explanation for the slight progressive decrease in the height of the epithelial cells in the fifteen, sixteen and eighteen day stages is probably twofold. In the first place, the cells may not have reached their full growth in width and hence are of necessity flattened out when the alveolus is becoming rapidly distended. In the second place the lumina of the acini in these stages are distended to their greatest capacity and the sheaths around them are stretched, it appears, to the limit. At the same time the lumina of the ducts are not so distended in the next stage; however, the ducts are more distended and the amount of secretion in the lumina of the acini seems to have decreased, a result progably brought about by the emptying of the secretion out of the acini into the ducts, thus relieving the pressure on the alveolar epithelial cells. This might permit the increase in height noted at nineteen days and twenty days.

It might be asked here how the acinus could increase in size, the lumina increase in diameter and at the same time the height of the epithelial cells remain practically constant without an increase in the number of these cells? This leads us to the question of mitoses in the gland which will be taken up later. But a count of thirty acini in each stage showed that the average number of cells around the lumina of the acini is eight,—the extremes in a single acinus being six and ten.

The explanation of the increase in the size of the acini with no increase in the number or decrease in the height of the epithelial cells, is that the cells enlarge, lose their high columnar form, widen out, and become low columnar or cuboidal. Thus the acinus can increase in size without an increase in the number of cells lining it, and with no marked change in absolute height.

The increase in the diameter of the entire alveolus is accounted for by the increase in the size of the lumen of the alveolus. The total increase from the thirteenth day to the twentieth day has been 10 microns, and in the same time the lumen has increased 11.7 microns. This discrepancy would probably disappear if a larger number of measurements on more specimens were taken.

The cytoplasm of the alveolar epithelium of the thirteenth day stage has a foamy appearance, which is due to the presence of a great many fine vacuoles. These vacuoles are for the most part small, round, discrete, and arranged irregularly throughout the cell. As mentioned, they are so great in number and so close together that they give the cytoplasm of the cell the appearance of a fine lacework. In many places some of these vacuoles are seen to be confluent.

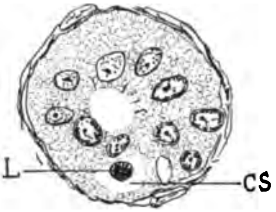

Fig. 107.—Acinus from the gland of a rat thirteen days pregnant. Many fine vacuoles in cytoplasm of the cells are shown. The section is tangential so some of the cells appear to have more than one nucleus. A lymphocytic-like nucleus is shown at *L*. Zenker's fixation; Cresyl violet stain; 6 microns. × 750.

By the fifteenth day the vacuolization of the cytoplasm is much more pronounced than in the thirteenth day stage. This appearance is due no doubt to the enlargement of the single vacuoles and the coalescence of many others. As yet there is no sign of any secretion in the lumen of the alveoli or ducts (Fig. 107).

The cytoplasm of the acinar cells in the sixteenth day and twelve hour stage shows merely an exaggeration of the condition in the previous stage, that is, the vacuoles in the cytoplasm are much larger.

In many places one observes what appears to be a "decapitation" of the cells, that is, a detachment of the inner portion adjacent to the lumen. Indeed, as mentioned in the review of the literature, some authors have held that the secretion of the mammary gland owes its origin, for the most part, to such a process.

A careful study of these cells shows, as a rule, one of two things. Either a portion of the section which has been poorly cut, or a location in which a secretion droplet is so large that it has ruptured the cell membrane and carried before it the inner end of the cell, or, rarely, even the nucleus.

With regard to the first possibility it should be emphasized that unless one is extremely careful in all the steps of his technic, the specimen will show various distortions and artefacts. In sections cut with a knife that is slightly dulled one will often get sections in which the whole epithelial lining of a duct is being displaced *en masse*, leaving the naked connective tissue behind, or alveoli will be fragmented and blood vessels ruptured. This, of course, would be an extreme case, but much less distortion might readily produce appearances of "decapitation" in the lining epithelial cells, a fact pointed out by O'Donoghue in the course of his work on the marsupials. In this connection it may be noted that if the tissue happens to be a piece of the gland imbedded while still attached to the skin, and it is cut so that the knife passes through the skin before it passes through the gland, there will be many artefacts which will not be present if the knife passes first through the softer glandular part of the tissue.

With regard to the second possibility, many of the cells contain secretion droplets larger than the nucleus of the corresponding cell. It would seem impossible for such large droplets to get out of the cell without doing at least some damage to the cell membrane. It must be borne in mind that here we are dealing with a condition different from that which obtains in certain mucous cells in which extremely large secretion droplets are formed. In the latter, the nucleus and cytoplasm are pushed to the base of the cell, and the cell membrane, if any, has a chance to regain its integrity before the cytoplasm can be extruded. In the mammary gland cell, however, some of the cytoplasm may be pushed ahead of the secretion droplet and forced out with it. Occasionally, as before mentioned, even the nucleus is carried ahead of the droplet.

Still another fact leads me to believe that this so-called "decapitation" process is accidental and not an essential part of milk formation, and that is, the relative scarcity of such appearances. Indeed the more perfect the section, the fewer of these decapitated cells appear.

In other places in the sixteen day stage one sees a seemingly ragged edge to some of the alveolar epithelial cells next to the lumen, an appearance which is probably due to an actual secretion being extruded from the cell. In this sixteen day stage, there is, in the lumina of the ducts and acini, quite an amount of secretion which is homogeneous, lightly staining, and containing many vacuoles, the result perhaps of dissolving out the fat contained in it.

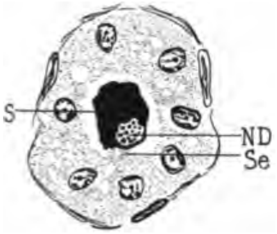

FIG. 108.

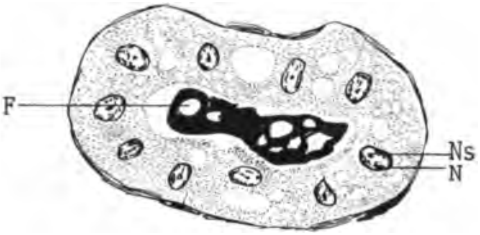

FIG. 109.

FIG. 108.—Acinus from the gland of a rat eighteen days and twelve hours pregnant. Cytoplasm much more vacuolated than in Figure 107. *S*, secretion mass; *ND*, nuclear (?) débris; *Se*, secretion being extruded from cell. Zenker's fixation; Cresyl violet stain; 6 microns. × 750.

FIG. 109.—Acinus from the gland of a rat nineteen days pregnant. Secretion mass with fat vacuoles, *F*, seen in lumen. This secretion shows characteristic arrangement of chromatin in nucleus, *N*. A well defined nucleolus, *Ns*, is shown. Zenker's fixation. Cresyl violet stain. 6 microns. × 750.

The cytoplasm of the acinar epithelial cells is very much more vacuolated in the eighteen day and 12 hour stage than in any of the stages previously described. There are many more of the vacuoles which are larger than the nucleus of the containing cell than there were in the preceding stage. There are also many more examples of secretion granules or droplets being extruded from the alveolar cells (Fig. 108).

In the lumina of the acini, besides the secretion already described, there is some granular débris which by its staining reaction with cresyl violet appears to be of nuclear origin. This débris perhaps comes from the nuclei which have been pushed out by the extremely large secretion droplets in the manner described in the foregoing stage.

Does this nuclear débris give rise to the nucleo-proteins of the milk? It undoubtedly contributes, at least in the stages studied, but as to whether or not it forms an essential constituent of the secretion I am unable to state.

By the nineteenth day the height of the secretory activity of the alveolar cells seems to have been reached, at least no further vacuolization of the cytoplasm is observed. From this stage up to within a few hours of delivery no changes in the cytoplasmic structure of the cells can be observed. There is abundant secretion present in the lumina of the ducts and acini (Fig. 109).

The nuclei of the acinar cells show no observable change during the period from the thirteenth day to within a few hours of birth. These nuclei are about 6.07 microns in diameter, an average of twenty measurements in each stage. Since they do not increase in size as the epithelial cell increases, they appear relatively smaller in the latter stages of pregnancy.

The chromatin of these nuclei has a very definite arrangement. The chromatin masses are arranged around the periphery of the nucleus and a well defined nucleolus in about the center (Fig. 109). This arrangement of the chromatin corresponds to that described by Szabo in the epithelial cells of the active mammary gland of guinea pigs.

Only two unquestionable instances of mitosis were observed in the stages studied. Both of these were in the thirteen day stage (Fig. 109). Furthermore, no definite evidence of amitosis could be observed. The absence of cell division, together with the fact that there is no increase in the number of cells about the alveoli in the stages studied, indicates that the gland has already reached its maximum growth, so far as number of cells is concerned, by the thirteenth day of pregnancy.

6. *Colostrum formation.*—In studying the epithelium of the ducts and acini, nuclei which resembled lymphocytic or leukocytic nuclei were observed in many places. These nuclei were apparently passing through the wall of the ducts and acini. Unfortunately none of the material used in this study had been fixed in Helly's fluid and hence no satisfactory Giemsa or Dominici stain could be used, which would have shown more clearly whether or not these nuclei belong to the blood elements.

There are, however, evidences indicating that these nuclei belong to cells of the wandering type. First, one must bear in mind that there is not a great deal of irregularity in the position of the epithelial nuclei of the ducts or acini, that is, they are about on the same level. These suspected nuclei, however, are usually seen either above or below the level of the epithelial nuclei. They are much smaller and much more densely staining than the nuclei of the epithelial cells, and their chromatin masses, although dense, have fairly definite outlines (Fig. 105). Occasionally they are surrounded by a clear space and in one case at least presented a definite, pale green, narrow rim of surrounding cytoplasm, in a section stained with cresyl violet.

Since these sections were stained with iron haematoxylin or cresyl violet, it is possible that the nuclei might be pycnotic epithelial nuclei. If they were, however, one would not expect to see the chromatin masses so clearly outlined and the whole nucleus should appear more uniformly shrunken and black in color. Their position, the appearance of their chromatin, and their relation to the epithelial cells, all point strongly to the conclusion that these nuclei belong to wandering cells.

There are other more general phenomena which support this conclusion. Leukocytic infiltration of the gland has been observed by various investigators in several other species, in the first half of pregnancy. The stroma is rich in cellular elements in the second half of pregnancy and (as noted in the literature) in several other forms leukocytes and lymphocytes have been found a constant constituent of colostrum.

So far as this study goes, all I am able to state is that my material does not prove that these nuclei are of the wandering cell type, but the appearance they present strongly indicates this conclusion. As previously mentioned, sections with specific blood stains must be carefully studied before a final conclusion is justified.

This leads to a consideration of the origin of colostrum corpuscles in the rat. In the lumina of the ducts, less often of the acini, in the latter stages of pregnancy fatty cells are observed which are lying free in the mass of secretion. These cells begin to appear in the sixteen day and twelve hour stage and increase in number from then until the end of pregnancy. Previous to the sixteen day and twelve hour stage a few desquamated epithelial cells were observed in the lumina of the ducts, but since they were not fatty they do not represent true colostrum corpuscles. The cells in the latter stages are in most cases as large as the epithelial cells of the gland; they have many fatty vacuoles, and the nucleus for the most part is large, round, and vesicular, appearing identical with the nuclei of the epithelial cells. In other cases, these cells are smaller, the cytoplasm is not quite so vacuolated, and the nucleus resembles that of a leukocyte or lymphocyte. A third class of these cells, which occur more rarely, resembles macrophages, in that they have a crescent shaped nucleus and abundant, lightly-staining cytoplasm, filled with a great many vacuoles. The various types of colostrum corpuscles may be seen in Figure 106.

What is the origin of these cells? I have already discussed the probability that the cells resembling lymphocytes and leukocytes might actually be such, which have wandered through the walls of the ducts and acini. Such cells, either in the lumina of these structures or before they pass through their walls, may have become laden with fat, although no fatty leukocytes were observed anywhere in the stroma.

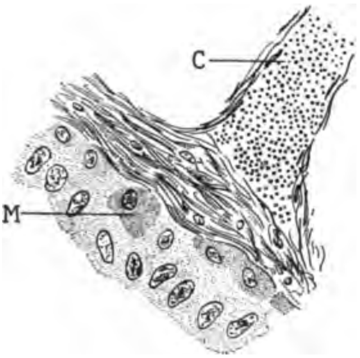

Fig. 110.—Portion of the wall of a duct of the gland of a rat nineteen days pregnant. A large cell, *M*, is seen in the wall of the duct. This cell has staining reaction different from that of the epithelial cells. The cell might possibly be a macrophage. *C* represents a greatly distended capillary. Zenker's fixation; Mallory's connective tissue stain; 7 microns. × 300.

The origin of those occasional cells which resemble macrophages, cannot be determined definitely. The different shape of the nucleus might be accidental or due to some degenerative process. However, Professor Downey, who kindly examined some of my preparations, called my attention to the presence of large, apparently phagocytic cells in the interalveolar spaces. A careful study with special stains might possibly show that these large phagocytes occasionally pierce the walls of the ducts or acini. The nuclei of the large interalveolar cells appeared rounded, however, rather than crescent shaped, as found in the intra-alveolar cells. But the nucleus is often variable in this type of cell (Fig. 110).

Most of the colostrum corpuscles, however, are undoubtedly desquamated cells derived from the epithelium of the ducts and acini. I have been able to trace them in all stages from the beginning of their desquamation to the time they have become rounded, fully formed colostrum corpuscles. Some appear breaking off from the epithelial wall but still partly attached. Others are lying close to the wall of the duct, but still maintaining a more or less cubical shape. Finally they appear as rounded cells, this shape being assumed when the cells become free in a liquid medium. These stages, may be seen in Figure 111.

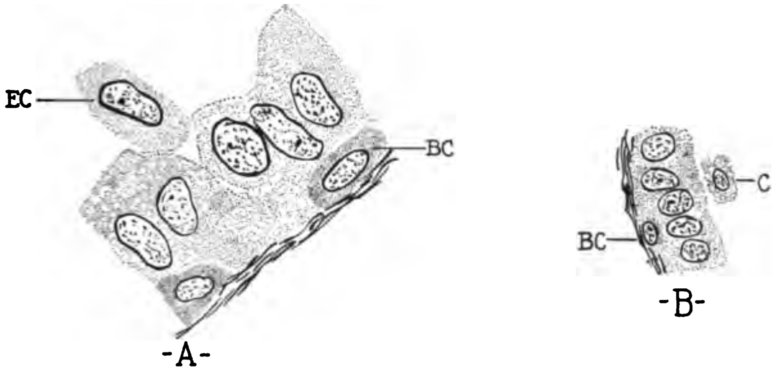

FIG. 111.—A section through the wall of a large duct of the gland from a rat eighteen days and twelve hours pregnant. Epithelial cell, *EC*, being desquamated. Basal cells shown at *BC*. *B*, wall of smaller duct from same section. Epithelial cell, *C*, shown free in the lumen; it has not yet lost its cylindrical shape. *BC*, basal cell. Zenker's fixation; Mallory's connective tissue stain; 6 microns. × 750.

Occasionally two adjacent cells may be detached at the same time, lying free in the lumen of the duct although still remaining attached to each other (Fig. 106).

Further evidence that these cells are epithelial in origin is shown by the fact that when they are observed in the ducts of the sixteen day and twelve hour stage they are not as vacuolated as they are later. In other words the cytoplasm of the earlier colostrum corpuscles is in the same condition as that of the epithelial cells lining the ducts. The nuclei, with the exception of the crescent shaped, and the smaller, probably leukocytic, nuclei, appear in most cases identical with the epithelial nuclei.

The scarcity of these cells in the lumina of the acini, indicates that by far the greater number of them come from the duct epithelium.

It should be emphasized that this desquamation of epithelial cells is not a pathologic condition, nor is it an artefact due to faulty technic I have excluded all cases in which there is an extensive desquamation of cells, or in which the walls of the ducts, acini, or blood vessels indicate a previous injury or abnormality. Only those cases were chosen for study in which the gland appeared perfectly normal in structure.

Before leaving the question of the origin of colostrum corpuscles, we may consider the theory of Steinhaus and Unger, according to which mast cells are thought to be transformed into colostrum corpuscles. Attention has already been called to the large number of mast cells in the stroma of the mammary gland of the albino rat during pregnancy. That this is a fairly constant occurrence in other forms, as well as in the rat, is indicated by the reports of Unger, Steinhaus, Michaelis, Berka, and Bizzozero and Ottolenghi.

Steinhaus, after describing the number and appearance of the mast cells in the mammary gland of the pregnant guinea pig, concludes that the colostrum corpuscles represent "einfach Mastzellen mit verfettenen eosinophilen Körnern." A close study of my data, however, fails to show a single mast cell undergoing fatty metamorphosis, or passing through the walls of the ducts or acini, or in the lumina of these structures. Furthermore the granules of mast cells are obviously not eosinophilic.

Unger is more definite in his statements regarding the relation of mast cells to colostrum. He found these cells in the glands of human beings and guinea pigs, in large numbers around the blood vessels and ducts, between the fat cells in the retromammary fat tissue, between the alveoli and sending up processes between the epithelial cells, in the perialveolar lymph and blood spaces, and in the axillary and retromammary lymph nodes. He claims to have demonstrated fat granules in the bodies of these cells, but other authors, particularly Bertkau and Berka have since questioned whether these cells were actually mast cells.

Unger concludes by approving Czerny's theory of the leukocytic origin of colostrum corpuscles, but goes farther in ascribing to the mast cells the major rôle in this process.

Berka, however, in discussing the theory, states that the mere presence of these mast cells in the gland during pregnancy does not prove that they aid in forming colostrum. Furthermore he was unable to demonstrate fat in any of the mast cells.

In the case of the rat, it is an easy matter to settle this question, for in the rat are mast cells in great numbers. Their distribution has already been described under stroma (Fig. 100).

If the mast cells take any part in the formation of colostrum, evidence should appear in the following respects: (1) If the mast cells undergo fatty metamorphosis, this process should appear even in ordinary stained sections, (2) some of these cells should be seen passing through the walls of the ducts or acini, and (3) some of them should be seen free in the lumina of these structures.

In a careful study of hundreds of sections, I have not seen a single mast cell undergoing fatty metamorphosis and in no case was a mast cell observed in the walls of the ducts or acini or within the lumina. It is therefore certain that in the rat at least, mast cells take no direct part in colostrum formation.

The picture presented, then, is one in which there is an increasing number of cellular elements in the secretion of the mammary gland as pregnancy advances. These cells present various stages of fatty vacuolization and represent true colostrum corpuscles. The following conclusions, therefore, appear justified on the basis of the evidence which has been presented:

1. Colostrum corpuscles in the rat are independent nucleated cells. This confirms the view of practically all modern investigators with the exception perhaps of Benda, who regards free cells in the lumina of the ducts and acini of the mammary gland as artefacts.

2. Colostrum corpuscles originate for the most part from desquamated epithelial cells. This agrees with the conclusions of Reinhardt, von Beuren, Will, Scanzoni, Sticker, Kehrer, Langer, de Sinety, Buchholz, Coen, Kadkin, and Palazzi, but disagrees with Rauber, Saefftigen, Czerny, Benda, Steinhaus, von Ebner, Unger, Cohn and Bab.

3. Some of the colostrum corpuscles may arise from immigrated lymphocytes or leukocytes. Palazzi, so far as I know, is the only author who calls specific attention to the double origin of colostrum corpuscles.

4. Mast cells play no direct part in the formation of colostrum corpuscles. This is in agreement with the conclusions of Cohn and Berka,[4] and opposed to the claims of Steinhaus and Unger.

TWO PRINCIPAL PHASES

The picture presented by the mammary gland of the albino rat in the latter part of pregnancy is that of a gland which has already reached its maximum growth, so far as a multiplication of elements is concerned. From the thirteenth day on, any enlargement is due chiefly to a mechanical distention of the hollow structures of the organ, together with hyperemia, although there is also hypertrophy of the glandular cells.

The gland is undergoing striking histologic changes, which are directed towards the elaboration of secretion. As a result, the parenchyma is the part of the gland that is changing, while the stroma (aside from the increased vascularity) remains practically unchanged, except secondary changes due to pressure associated with the growth and expansion of the parenchyma.

The secretory activity of the gland is evidenced by a hypertrophy of the glandular elements. The acini increase in size, their lumina enlarge, and their epithelial cells become much larger. The cytoplasm of the epithelial cells becomes progressively vacuolated, first in those of the acini, and later in those lining the ducts. The cells remain clearly outlined and do not lose their definite form, and the nuclei do not change in position or appearance. These facts indicate that the cytoplasmic vacuolization is the result of the secretory activity of the cell, and is not a sign that the cell is undergoing fatty metamorphosis or necrobiosis.

Two stages can therefore be recognized in the changes of the mammary gland of the albino rat during pregnancy. These two phases, as described by Bouin and Ancel and Schil, in the rabbit, are (*a*) a phase of growth activity, and (*b*) a phase of secretory activity. The first, which occurs in stages earlier than those covered in the present paper, is marked by the addition of new elements, an increase in the number of ducts and lobules, and an infiltration of lymphocytes and leukocytes. The second phase begins in the latter half of pregnancy, the period studied in the present investigation. Here the epithelial cells begin to elaborate secretion and from now on any growth is due chiefly to cellular hypertrophy and enlargement by accumulation of secretion and by hyperemia. At the same time the leukocytic infiltration is becoming progressively less prominent. The formation of colostrum also falls within this period.

SUMMARY

The conclusions from a study of the mammary gland in the albino rat from the thirteenth to the twentieth day, or end of pregnancy, may be summarized briefly as follows:

1. The nipple increases in size during pregnancy, but has apparently reached its maximum growth by the thirteenth day. The

epithelial hood about the nipple entirely disappears during pregnancy, resulting in an elongation of the nipple, and at the same time the smooth muscle about the main duct has become well developed.

2. The stroma, aside from progressive increase in the blood vessels, and an increase in the elastic tissue, especially around the ducts, shows no marked changes. There is no membrana propria around the acini, aside from a thin connective tissue sheath formed by their distention.

3. There is a tremendous proliferation of the mammary parenchyma during pregnancy. Hyperplasia is evidently confined chiefly to the first half of pregnancy, as mitosis is rare from the thirteenth day and amitosis apparently absent. The ducts and acini continue to increase in size, however, partly through hypertrophy of the epithelial cells, and partly by accumulation of secretion within the lumina.

4. Progressive cytoplasmic vacuolization, indicating secretory activity, is apparent in the acinar epithelium from the thirteenth day, and some days later in the cells lining the ducts. The maximum degree of vacuolization is reached by the nineteenth day. "Decapitation," or detachment of the inner portion of the acinar cells during secretion, is a rare occurrence and does not represent the usual mode of secretion in the stages observed. The secretory cells usually remain intact.

5. Colostrum corpuscles are derived chiefly from desquamated epithelial cells of the ducts and acini. Some may be derived from immigrated lymphocytes or leukocytes. Mast cells are abundant in the stroma, but take no direct part in the formation of colostrum corpuscles.

BIBLIOGRAPHY

1. Bab, H.: Die Colostrumbildung. Diss., Berlin, 1904, 240 pp.

2. Benda, C.: Das Verhältnis der Milchdrüse zu den Hautdrüsen. Dermat. Ztschr., 1894, i, 94–110.

3. Berka, F.: Ein Beitrag zur Anatomie und Physiologie der Milchdrüse. Anat. Anz., 1907, xxx, 161–180.

4. Berka, F.: Die Brustdrüse verschiedener Altersstufen und während der Schwangerschaft. Frankfurt. Ztschr. f. Path., 1911, viii, 203–256.

5. von Beuren, R. L.: Die Entwickelung der Formbestandteile der Milch. Nederl. Lancet, 1849. Quoted by Michaelis, by Bab, and by Bizzozero and Ottolenghi.

6. Bierich, R.: Untersuchungen über das elastische Gewebe der Brustdrüse im normalen Zustande und bei Geschwülsten. Diss., Königsberg, 1900, 19 pp.

7. Bizzozero and Ottolenghi: Histologie der Milchdrüse. Ergebn. f. Anat. u. Entw., 1899, ix, 259–266.

8. Buchholz, W.: Das Verhalten der Colostrumkörper bei unterlassener Säugung. Göttingen, Kaestner, 1877, 20 pp.

9. Bouin, P. and Ancel, P.: Sur l'évolution de la glande mammaire pendant la gestation; determinisme de la phase glandulaire gravidique; (note préliminaire). Compt. rend. Soc. de biol., 1912, lxxii, 129–131.

10. Coen, E.: Beiträge zur normalen und pathologischen Histologie der Milchdrüse. Beitr. z. path. Anat. u. Physiol., 1888, ii, 83–100.

11. Cohn, M.: Ueber Frauenmilch. Münch. med. Wchnschr., 1900, xlvii, 753.

12. Czerny, A.: Ueber die Brustdrüsensecretion beim Neugeborenen und über das Verhältniss der sogenannten Colostrumkörperchen zur Milchsecretion. Paediat. Arb. Berlin, 1890, 194–226.

13. Duclert, L.: Étude histologique de la sécretion du lait. Montpellier, These, 1893, 79 pp. Quoted by O'Donoghue and by Bizzozero and Ottolenghi.]

14. von Ebner, V.: Kölliker's Gewebelehre. 6 ed., 1896, iii, 593.

15. Frank, R. T. and Unger, A.: An experimental study of the causes which produce the growth of the mammary gland. Arch. Int. Med., 1911, vii, 812–838.

16. Heidenhain, R.: Die Milchabsonderung. Hermann's Handbuch der Physiologie, Leipzig, 1880, 374–406.

17. Kadkin: Beiträge zur Anatomie der Milchdrüsen während ihrer Tätigkeit]. Diss., Petersburg., 1890. Review in Jahresb. u. Anat. u. Physiol., 1891, xx, 481.

18. La Croix, E.: De l'existence de cellules en paniers dans l'acinus et les conduits excreteurs de la glande mammaire. Compt. rend. Acad. d. sc., 1894, cxix, 748–751.

19. Lane-Claypon and Starling, E. H.: An experimental inquiry into the factors which determine the growth and activity of the mammary glands. Proc. Roy. Soc. Lond., 1905–1906, Sec. B., lxxvii, 505–522.

20. Langer, C.: Die Milchdrüse. Stricker's Handbuch der Lehre von den Geweben, 1871, i, 627–634.

21. Michaelis, L.: Beiträge zur Kenntniss der Milchsecretion. Arch. f. mikr. Anat., 1898, li, 711–747.

22. Myers, J. A.: Studies on the mammary gland. I. The growth and distribution of the milk-ducts and the development of the nipple in the albino rat from birth to ten weeks of age. Am. Jour. Anat., 1916, xix, 353–390.

23. Myers, J. A.: Studies on the mammary gland. II. The fetal development of the mammary gland in the female albino rat. Am. Jour. Anat., 1917, xxii, 195–224.

24. Myers, J. A.: Studies on the mammary gland. IV. The histology of the mammary gland in male and female albino rats from birth to ten weeks of age. Am. Jour. Anat., 1919, xxv, 395–435.

25. Myers, J. A.: Studies on the mammary gland. V. The effects of inanition on the developing mammary glands in male and female albino rats from birth to ten weeks of age. Am. Jour. Dis. Child., 1919, xvii, 311–328.

26. Myers, J. A.: Studies on the mammary gland. VII. The distribution of the subcutaneous fat and its relation to the developing mammary glands in male and female albino rats from birth to ten weeks of age. Abstract: Anat. Rec., 1919, xvi, 159–160.

27. O'Donoghue, C. H.: The growth-changes in the mammary apparatus of *Dasyurus* and the relation of the corpora lutea thereto. Quart. Jour. Micr. Sc., 1911, n.s., lvii, 187–234.

28. Palazzi, G.: Sopra alcune differenze microscopische fra la secrezione mammaria durante la gravidanza e quella finito l'allatamento. Ann. di ostet., 1894, xvi, 425–455.

29. Rauber, A.: Bemerkungen über den feineren Bau der Milchdrüsen. Schmidt's Jahrb., 1879, clxxxii, 7–8.

30. Reinhardt, B.: Ueber die Entstehung der Körnchenzellen. Virchows Arch. f. path. Anat., 1847, i, 20–71.

31. Saefftigen: Zur feineren Anatomie der Milchdrüsen während der Lactationsperiode. Bull. de l'Acad. imp. d. sc. de St. Petersbourg, 1881, xxviii, 78: Quoted by Bab and by Szabo.

32. Scanzoni: Ueber die Milksecretion und die entzündlichen Anschwellungen der Brustdrüsen bei Neugeborenen. Verhandl. der physic.-med. Gessellschaft in Würzburg, 1855, ii, 302.

33. Schil, L.: Recherches sur la glande mammaire; sur les phases qu'elle présente au cours de son évolution et leur determinisme Nancy, 1912, 263 pp.

34. de Sinety, M.: Recherches sur la mamelle des enfants nouveaux-nés. Arch. de phys. norm. et pathol., 1875, ii, 291–302. Quoted by Bizzozero and Ottolenghi.

35. Steinhaus, J.: Die Morphologie der Milchabsonderung. Arch. f. Physiol., 1892, Suppl.-Bd., 54-68.

36. Sticker, A.: Zur Histologie der Milchdrüse. Arch. f. mikr. Anat., 1899, liv, 1–23.

37. Szabo, J.: Die Milchdrüse im Ruhezustand und während der Secretion. (Transl. from: Magyar orvosi Arch., 1896, v). Pest. med.-chir. Presse, 1897, xxxiii, 965

38. Unger, E.: Das Colostrum. Virchows Arch. f. path. Anat., 1898, cli, 159–175.

39. Wahl, H. M.: Development of the blood vessels of the mammary gland in the rabbit. Am. Jour. Anat., 1915, xviii, 515–524.

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A NOTE ON THE RELATION BETWEEN THE WEIGHT OF THE THYROID AND THE WEIGHT OF THE THYMUS IN MAN

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In a recent publication Dustin and Zunz (1) have recorded some interesting observations on the weight of the thyroid and the thymus in early maturity. Their data are quite unique, consisting of weighings of the thyroids and thymi of thirty-eight individuals who, with one exception, died within forty-eight hours after receiving wounds in battle, and who came to autopsy within twelve hours or less after death. We are thus furnished with a series of records of the weight of the thymus in presumably normal young adults which greatly improves our knowledge of the later ponderal changes of this organ.

Dustin and Zunz have analyzed this material by means of tabulations and a graph in which the thymus weight is plotted against the thyroid weight. They found a negative correlation between thymus weight and thyroid weight in man, and they conclude that their results support the experimental findings of Gley (2) and others who have observed an increase in the thymus following thyroidectomy in amphibia.

Although this series of cases is very small for any statistical study, its unique character and the importance of the conclusions which have been drawn from its examination seem to warrant its further analysis by some of the simpler biometric methods. Accordingly, the standard deviation and the coefficient of variation have been determined for the thymus and thyroid in the series and also the coefficient of correlation between the two organs. These determinations were first made for the entire series of cases as given in the original article, and second for the same series with the omission of four cases which seem to be of doubtful value.

In the complete series the average weight of the thyroid is 32.0 ± 2.4 grams, the standard deviation 21.8 grams, and the coefficient of variation 0.68. The average thymus weight is 15.6 ± 0.7 grams, the standard deviation 7.07 grams and the coefficient of variation 0.45. The coefficient of correlation between the thyroid and the thymus is −0.265 with a probable error of ±0.102.

The second calculation was made from the series after the omission of the following cases.

Case 1, in which the weight of the thyroid was 134.54 grams, nearly four times the average weight of the group and over two times the weight of the next member of the series. It can scarcely be doubted that this great enlargement was associated with thyroid disease.

Cases 2 and 11, in which there was a complete involution of the thymus. As these cases were individuals aged twenty-five and twenty-eight years, respectively, it is most probable that the thymi had undergone accidental involution, presumably in some previous illness.

Case 38 was a youth but fourteen years old and cannot be properly included with a series of young adults, since the thymus undergoes profound weight changes in adolescence.

In the selected series, with these four cases omitted, the average thyroid weight was 26.6 ± 1.41 grams, the standard deviation 12.26 grams, and the coefficient of variation 0.45. The average weight of the thymus was 16.2 ± 0.64 grams, the standard deviation 5.49 grams, and the coefficient of variation 0.33. The coefficient of correlation of the thyroid and thymus was −0.156 with a probable error of ±0.107.

These calculations show a negative correlation between the weight of the thyroid and the weight of the thymus in the complete series, as Dustin and Zunz suspected. But this correlation is so low and the probable error is so large that we are hardly justified in attaching any particular significance to it. This seems the more probable since when the four cases which are of very doubtful value are omitted the correlation drops to from −0.265 to −0.156 and the probable error remains almost unchanged. A slight negative correlation might well exist between the two organs, since the thyroid follows the scheme of general body growth and increases a little in weight during the third decade, while the thymus decreases in absolute as well as relative weight after early adolescence. But this negative correlation does not warrant the assumption of a functional relation between the two organs; a similar correlation might be expected between the thymus and any of the viscera which follow the general scheme of the growth in mass of the body as a whole.

In order to test this relation in another way I have calculated the coefficient of correlation of the thyroid and thymus in a series of twenty-five full-term newborn children. The data for this series were taken in part from the lists of cases reported by Valtorta (3) and Lomer (4) and in part from my own records. The average weight of the thyroid in this series was 3.4±0.24 grams, the standard deviation 1.8 grams, and the coefficient of variation 0.53. The average thymus weight was 14.2±0.90 grams, the standard deviation 6.7 grams, and the coefficient of variation 0.47. The coefficient of correlation of the thymus and thyroid was +0.19 with a probable error of ±0.08. Thus in the newborn, as in the adult, the variability of the thymus and the thyroid is very great and the correlation between the two organs is quite small. But, in contrast to the adult, the slight correlation which does exist in the newborn is a positive one.

These figures indicate that any correlation which may exist between the weights of the thyroid and the thymus is inconstant in postnatal life, and they offer little if any support to the concept of a direct functional relation between the two organs.

LITERATURE CITED

1 Dustin, A. P., et Zunz, E. 1918 A propos des corrélations fonctionnelles entre le thymus et le corps thyroïde. Journ. de Physiol. et de Pathol. Gen., T. 17, pp. 905–911.

2 Gley, E. 1909 Glande thyroïde et thymus. C. R. Soc. Biol. Paris, T. 66, p. 1007.

3 Valtorta, F. 1909 Richerche sullo sviluppo dei visceri del feto. La individualita nel neonato. Ann. Ostet. e Ginecol., T. 31, pp. 673–713.

4 Lomer 1889 Ueber Gewichtsbestimmung der einzelnen Organe Neugeborener. Zeitschr. f. Geburtsh. u. Gynäkol., Bd. 16, S. 106–130.

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A SIMPLE TRACING APPARATUS FOR MAKING TOPOGRAPHIC RECONSTRUCTIONS

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THREE FIGURES

The study of certain phases of the anatomy of the fetus and infant is hindered somewhat by the lack of any simple method of making topographic reconstructions of the various organs and regions. Graphic reconstruction from microscopic sections, which is so successful in embryologic work, is generally impracticable here, for the preparation of even a few sets of serial sections of this material requires an almost prohibitive amount of time and labor, and the thorough decalcification necessary for the larger specimens usually causes serious shrinkage and distortion in the process of embedding. The usual methods employed in the study of adult topography are also inadequate for this work. Topographic reconstructions of the adult are generally made either by graphic reconstruction from free-hand transverse sections after the method first suggested by Henke or by plotting from fixed points which are established by setting long pins or skewers in the body in certain definite positions before dissection is begun. But to make accurate reconstructions of the smaller structures of the fetus and infant the sections must be cut so thin that they are extremely fragile and subject to distortion. And the fixed point method is very inconvenient both because of the difficulty in placing the pins firmly in position in the delicate tissues and because these pins make the subsequent dissection of the smaller regions almost impossible.

The apparatus which is described here was devised to overcome some of these difficulties, and after a considerable trial has been found sufficiently useful to warrant the publication of an account of it. It consists essentially of a tracing stand, covered by a glass grating, and an eyepiece.

The stand is shown in figure 1. Its base is a slab of hardwood, 25 inches long, 17 inches wide, and 1.5 inches thick. Seven inches above this base is a sheet of heavy plate glass inclosed in a strong hardwood frame, which is supported at its corners by four brass rods. At one end these rods or legs are connected with the frame by hinges and firmly attached to the base-board with screws. At the other their upper ends are screwed to the frame of the plate, but their lower ends are covered by rubber caps which rest freely on the base-board. This permits the frame to be raised so that large objects may be easily placed on the base-board below.

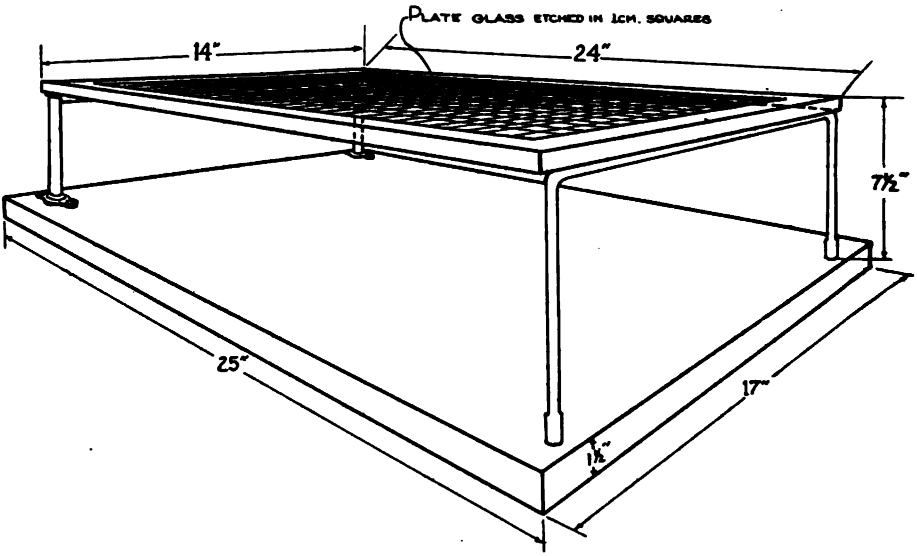

Fig. 1 Stand of reconstruction apparatus.

The glass plate is ruled with a centimeter grating and the lines of this grating are numbered or lettered consecutively at its margin. The middle longitudinal and the middle cross line of the grating are ruled a little heavier than the others and are filled with pigment to distinguish them as base lines (fig. 3).

The eyepiece is a brass tube 4 inches long and 0.8 inch in diameter (fig. 2, *A*). Its upper end is closed by a screw cap which contains a central pinhole opening (fig. 2, *B*). At the bottom of the tube are cross-hairs of spun glass or very fine wire which are set a little above its lower opening and cross in the optical axis of the tube directly in line with the pinhole opening in the cap. The lower end of the tube is set in the center of a circular plate of brass 2.4 inches in diameter and 0.2 inch thick. One quadrant of this base is cut away, its margins being so adjusted that they fall directly in line with the cross-hairs of the eyepiece.

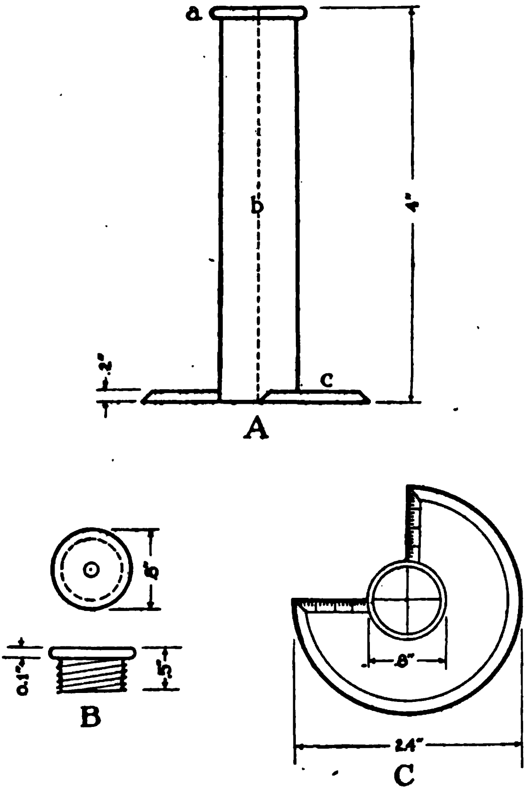

Fig. 2 Eyepiece of reconstruction apparatus. *A*, entire eyepiece; *B*, detail of screw cap with pinhole opening; *C*, detail of quadrant base.

The edges of the quadrant are beveled and are graduated in millimeters, the zero points of the scales lying exactly 1 cm. from the optical center of the eyepiece (fig. 2, *C*).

The method of using the apparatus is simple. The specimen to be reconstructed is fixed firmly in a tray or better set in a base of plaster of Paris or hard wax. It is then placed on the base-board and adjusted so that its midline corresponds approximately with the midline of the grating on the glass plate above it. Orientation points are then established by marking the specimen with dots of indelible ink or by setting small pins in it. At least three such points should be established as far apart as possible and in regions which will not be disturbed in the course of the subsequent dissection. A large sheet of coördinate paper is now numbered to correspond with the numbering of the grating, and base lines corresponding to those of the grating are drawn upon it. The exact position of the orientation points and the outlines and superficial landmarks of the specimen are now determined by successive readings with the eyepiece which is passed over the grating. As these determinations are made they are recorded in their proper places on the coördinate paper, and the first plot giving the outlines of the specimen is completed by connecting these points. After the outline is made the specimen may be dissected layer by layer and as the different structures are exposed they may be outlined in their proper positions on the plot by replacing the specimen under the grating, adjusting the orientation points to their recorded positions, and taking the necessary readings with the eyepiece. With a little practice this process can be carried out quite rapidly. Readings with the eyepiece to half-centimeters can be made directly from the lines of the grating and readings to half-millimeters by using the scales on the margins of the quadrant. The specimen should be strongly illuminated when the readings are made. Orthographic projection is assured by the use of the eyepiece with a vertical optical axis established by the pinhole opening and cross-hairs. It is possible to make the reconstruction at any magnification desired by modifying the scale of the coördinate paper.

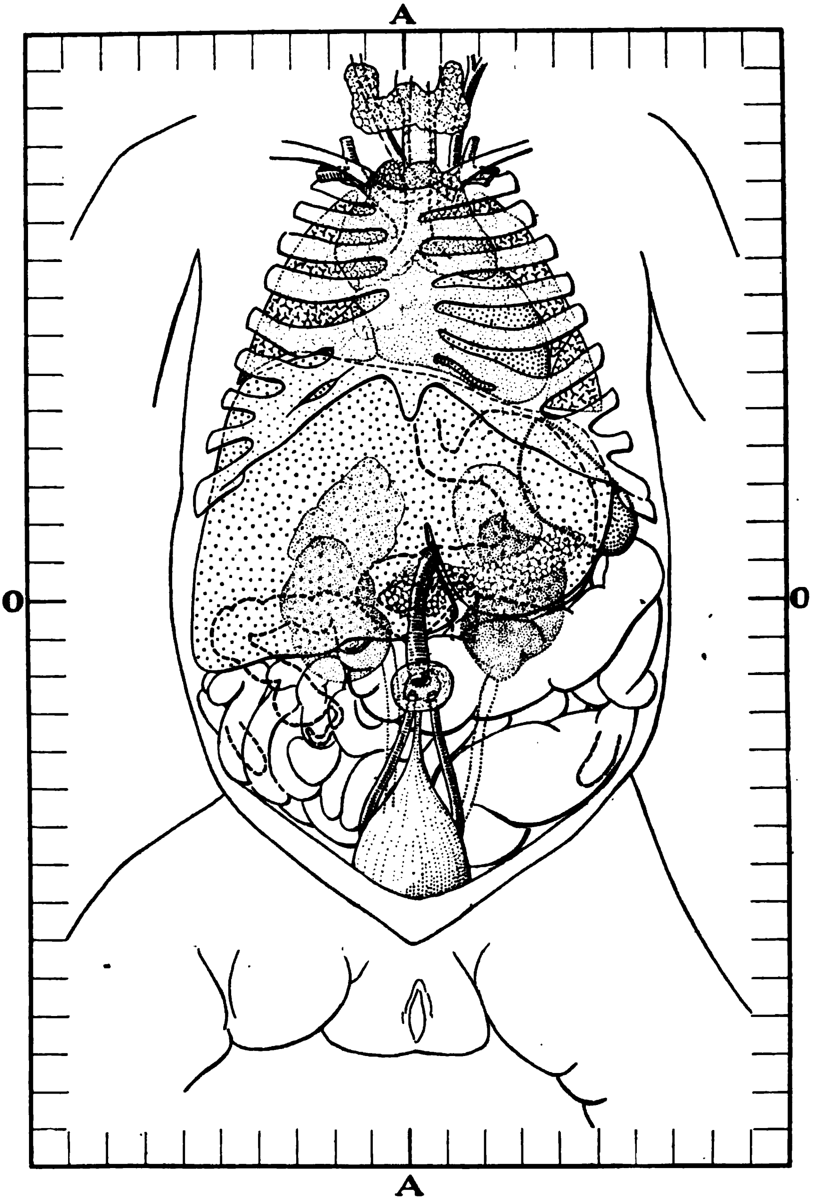

Fig. 3 Reconstruction of the abdominal and thoracic viscera of a full-term newborn infant. Made by H. J. Bower and W. C. Stillwell with the apparatus herein described. The reconstruction has been retraced and reduced to one-half the original (natural) size. The centimeter scale of the grating is shown at the margins of the drawing. *A–A'* and *O–O* are the longitudinal and cross base-lines.

The chief sources of error in making reconstructions of this kind are due, first, to changes in the form of the specimen which may occur in the course of dissection and, second, to variations caused by the improper adjustment of the eyepiece. The first may be avoided, in a great measure, by partially embedding the specimen in a firm base of plaster or wax as mentioned above and by care in dissection. The second can be entirely eliminated if care is taken to see that the margins of the quadrant are either parallel or at right angles to the lines of the grating before each reading is made.

An example of a reconstruction by this method of the thoracic and abdominal viscera of a full-term stillborn infant is shown in figure 3. The original plotting has been retraced and inked, the published figure being one-half the size of the original.

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67 (1814)

On the weight increments of premature infants as compared with those of fetuses of the same gestation age and those of full-term children.

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One method of approaching the problem of the effect of birth and the postnatal environment on the course of human growth is by the comparison of the rates of growth of premature infants with the growth rates of fetuses of the same gestation age and with those of full-term children. If the environmental factors are the all-important ones it might be expected a priori that the rate of growth of prematures would agree, in the main, with that of full-term children. If, on the other hand, the effects of the extrauterine environment do not seriously modify the course of growth established in prenatal life, it is to be expected that the curve of rate of growth in prematures will follow in general that of the fetus of the same gestation age.

The following study was based upon the weight records of 78 premature infants. In collecting the histories all cases were included which made any gain in weight in the first month after birth. These cases were divided in four groups according to their birth weight, and the rate of growth in the form of the monthly percentage increment in weight was determined separately for each case. The mean monthly increment of each groud for each month was then determined by averaging these individual percentages. The results obtained are shown in the table below. It will be noted: first, that the percentage increment in weight of prematures in the first postnatal month is lower than in the second month, and that following the second month the rate of increment gradually decreases; and, second, the percentage increments are in a general way inversely proportional to the birth weight.

AVERAGE MONTHLY PERCENTAGE INCREMENTS IN BODY-WEIGHT OF PREMATURE AND FULL-TERM CHILDREN IN INFANCY.

	Group.			
	A	B	C	D
Range in birth-weight (grams)	1,000 to 1,500	1,500 to 2,000	2,000 to 2,500	ca. 2,750 to ca. 4,200
Approximate average birth weight (grams)	*1,300*	*1,720*	*2,300*	*3,380*
Total number of cases	17	35	26	*
Average percentage increment in:				
First month	22.8	16.8	13.8	21.2
Second month	45.1	31.6	26.7	19.4
Third month	24.5	20.4	15.5	14.6
Fourth month	21.1	17.2	13.5	11.4
Fifth month	16.2	13.6	—	8.9
Sixth month	14.4	—	—	5.8
Seventh month	11.6	—	—	5.9
Eighth month	7.4	—	—	3.9
Ninth month	5.1	—	—	4.0

* Average of ten large published series of observations.

The increments thus determined were next compared with those of fetuses of the same gestation age and with those of full-term newborn children.

The norm for fetal growth in weight was estimated from the following empirical formulæ: (1) $Y = 0.24\,X^{3.2} + 400$, where Y is the body-weight in grams and X is the body length in cm., and (2) $Y = 8.9\,(X - 1) - 0.27\,(X - 1)^2 - 6.5$, where Y is the body length in cm. and X is the age in fetal or lunar months. The norm for weight increment in the first nine postnatal months was determined by calculation from 10 large series of published averages on the increase in body weight in the first year. When the monthly weight increment rates of the premature infants are compared with these norms it is found that they fall much closer to the calculated rates of growth of fetuses of the same size and age than to those of newborn children. This is shown particularly well by group A of the smallest prematures which were approximately 7 fetal months old when born. The comparison is shown graphically in the chart below.

These results indicate that premature children, after a short period of retarded growth incident to the adjustment to the extrauterine environment, tend to regain the fetal rate of growth and to follow this course of growth until some time in the latter part of the first year when the rates of fetal and postnatal growth approximate one another. In other words the growth tendency of prematures is in general that of fetuses of the same size and age rather than that of full-term children. These results are in agreement with those of Hammett[1] on growth capacity and body weight in the first two weeks of postnatal life, and with certain findings of Cammerer,[2] but seem to be in opposition to some of the conclusions of Schwarz and Kohn[3] and of Ylppö.[4] That this opposition is apparent rather than real will be shown in a later communication.

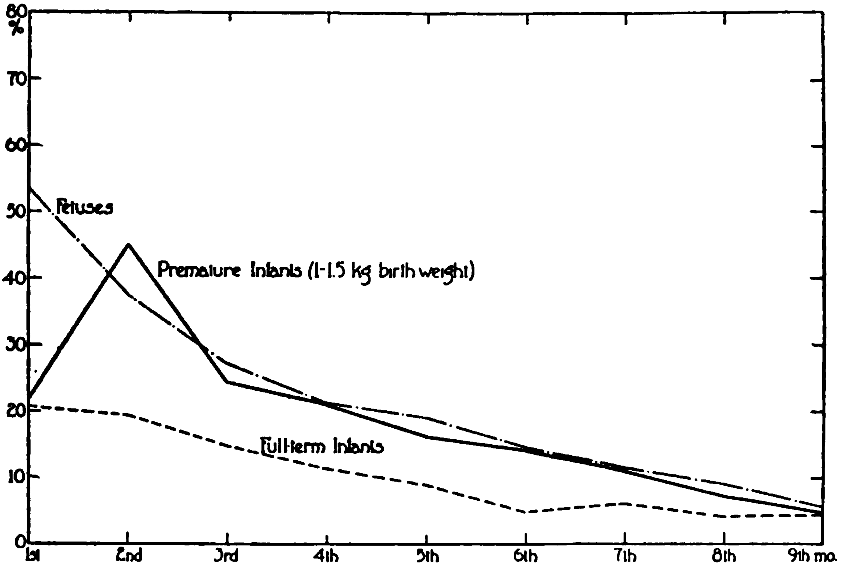

FIG. 1. A graph showing monthly percentage increment in weight of a group of premature infants ranging from 1.0 to 1.5 kg. in birth weight. The solid line represents the rate of increment of the premature children in the first 9 months after birth. The upper broken line represents the calculated rate of increment of the fetuses of the same size and age as the prematures. The lower broken line represents the rate of increment of full-term children.

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[1] Hammett, F. S., *Amer. Jour. Physiol.*, 1919, xlv, 396.

[2] Cammerer, W., *Jahrb. f. Kinderheilk.*, 1900, liii, 381.

[3] Schwarz and Kohn, J. L., *Amer. Jour. Dis. Children*, 1921, 296.

[4] Ylppö, *Zeitschr. f. Kinderheilk.*, 1919, xxiv, 179.

INTRODUCTION

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ANATOMY, as the term is usually employed, denotes the study of the structure of the human body. Properly, however, it has a much wider significance, including within its scope not man alone, but all animal forms, and, indeed, plant forms as well; so that, when its application is limited to man, it should be termed human anatomy. *Human anatomy*, then, is the study of the structure of the human body, and stands in contrast to, or rather in correlation with, *human physiology*, which treats of the functions of the human body, the two sciences, anatomy and physiology, including the complete study of man's organization and functional activities.

In the early history of the sciences these terms sufficed for all practical needs, but as knowledge grew, specialization of necessity resulted and new terms were from time to time introduced to designate special lines of anatomical inquiry. With the improvement of the microscope a new field of anatomy was opened up and the science of *histology* came into existence, including the portion of anatomy which deals with the minuter details of structure. So, too, the study of the development of the body gradually assumed the dignity of a more or less independent study known as *embryology*, and the study of the structural changes due to disease was included in the science of *pathology;* so that the term anatomy is sometimes limited to the study of the macroscopic structure of normal adult organisms.

It is clear, however, that the lines of separation between anatomy, histology, embryology, and pathology are largely arbitrary. Microscopic anatomy necessarily grades off into macroscopic anatomy; the development of an organism is a progressive process and the later embryonic or fetal stages shade gradually into the adult; and structural anomalies lead insensibly from the normal to the pathological domains. Furthermore it is found that in its individual development the organism passes through stages corresponding to those of its ancestry in evolution; in other words, ontogeny repeats phylogeny. A comprehensive study of anatomy must therefore include more or less of the other sciences. Since an appreciation of the significance of structural details can be obtained only by combining the studies of anatomy (including histology) and embryology, and since, further, much light may be thrown on the significance of embryological stages by comparative studies, anatomy, embryology, and comparative anatomy form a combination of sciences by which the structure of an organism, the significance of that structure, and the laws which determine it are elucidated. For this combination it is convenient to have a single term, *morphology*, a word meaning literally the science of form.

In morphological comparisons the term *homology* denotes similarity of structure, due to a common origin in the evolution of organs or parts; while *analogy* denotes merely physiological correspondence in function. Thus the arm of man and the wing of a bird are homologous, but not analogous, structures; on the other hand, the wing of a bird and the wing of an insect are analogous, but not homologous. *Serial homology* refers to corresponding parts in successive segments of the body.

Nomenclature.—Formerly there was much confusion in the anatomical nomenclature, due to the multiplicity of names and the lack of uniformity in using them. Various names were applied to the same organs and great diversity of usage prevailed, not only between various countries, but also even among authors of the same country. Recently, however, a great improvement has been made by the general adoption of an international system of anatomical nomenclature. This system was first adopted by the German Anatomical Society at a meeting in Basel, in 1895, and is hence called the Basel Nomina Anatomica, or briefly, the BNA. The BNA provides each term in Latin form, which is especially desirable for international usage. Each nation, however, is expected to translate the terms into its own language, wherever it is deemed preferable for everyday usage. Thus in the present work the Anglicised form of the BNA i generally used. Where not identical, however, the Latin form is added once fo each term in a place convenient for reference, and is designated by enclosure i brackets [ ]. Where necessary the older terms have also been added as synonyms

The Commission by whom the BNA was prepared included eminent anatomists represen ing various European nations. The work of the Commission was very thorough and carefu and extended through a period of six years. Among the guiding principles in the difficult tas of selecting the most suitable terms were the following: (1) Each part should have one nan only. (2) The names should be as short and simple as possible. (3) Related structur should have similar names. (4) Adjectives should be in opposing pairs. A few exceptio were found necessary, however.

On account of its obvious merits, the BNA system has been generally adopted througho the civilized world, and the results are very satisfactory. Comparatively few new terms hav been thereby introduced, over 4000 of the 4500 names in the BNA corresponding almost exact to older terms already in use by the English-speaking nations. Certain minor defects hav been criticized; but these are outweighed by the advantages of this uniform system.

Abbreviations.—Certain frequently used words in the BNA are abbreviated as follow a., arteria (plural, aa., arteriæ); b., bursa; g., ganglion; gl., glandula; lig., ligamentum (plura ligg., ligamenta); m., musculus (plural, mm., musculi); n., nervus (plural, nn., nervi); oss ossis (or ossium); proc., processus; r., ramus (plural, rr., rami); v., vena (plural, vv., venæ).

Terms of position and direction.—The exact meaning of certain fundamenta terms used in anatomical description must be clearly understood and kept i mind. In defining these terms, it is supposed that the human body is in a upright position, with arms at the sides and palms to the front.

The three **fundamental planes** of the body are the sagittal, the transverse an the frontal. The vertical plane through the longitudinal axis of the trunk dividing the body into right and left halves, is the *median* or *midsagittal* plane and any plane parallel to this is a *sagittal* plane. Any vertical plane at righ angles to a sagittal plane, and dividing the body into front and rear portions is *frontal* (or coronal) plane. A plane across the body at right angles to sagittal an coronal planes is a *transverse* or *horizontal* plane.

Terms pertaining to the front of the body are *anterior* or *ventral;* to the rea *posterior* or *dorsal;* upper is designated as *superior* or *cranial;* and lower as *inferic* or *caudal.*

The term *medial* means nearer the midsagittal plane, and *lateral*, further fror that plane. These terms should be carefully distinguished from internal (inner and external (outer), which were formerly synonymous with them. *Internal*, a now used (BNA), means deeper, i. e., nearer the central axis of the body or part while *external* refers to structures more superficial in position. *Proximal*, i describing a limb, refers to position nearer the trunk; while *distal* refers to a mor peripheral position.

Adverbial forms are also employed, e. g., anteriorly or ventrally (forward, before); post riorly or dorsally (backward, behind); superiorly or cranially (upward, above); and inferiorl or caudally (downward, below).

It should also be noted that the terms ventral, dorsal, cranial and caudal are independent the body posture, and therefore apply equally well to corresponding surfaces of vertebrates i general with horizontal body axis. On this account these terms are preferable, and will doub less ultimately supplant the terms anterior, posterior, superior and inferior.

The discrimination in the use of several similar terms of the BNA should also receive atte tion. Thus *medianus* (median) refers to the median plane. *Medialis* (medial) means near the median plane and is opposed to lateral, as above stated. *Medius* (middle) is used to desi nate a position between anterior and posterior, or between internal and external. Betwe medialis and lateralis, however, the term *intermedius* is used. Finally, *transversalis* mea transverse to the body axis; *transversus*, transverse to an organ or part; and *transversariu* pertaining to some other structure which is transverse.

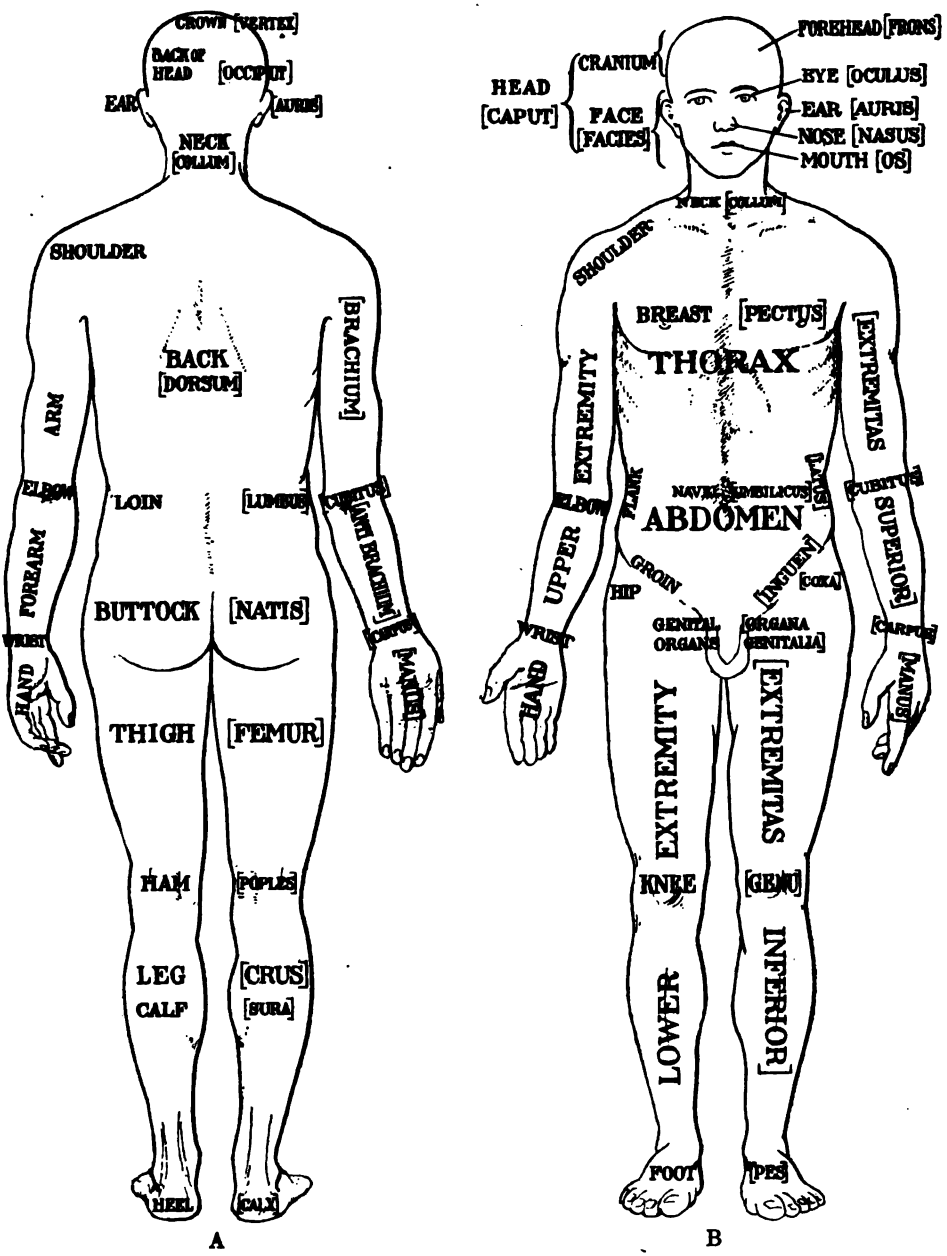
Parts of the body.—The primary divisions of the human body (fig. 1) are th head, neck, trunk and extremities. The *head* [caput] includes *cranium* and *fa* [facies]. The *neck* [collum] connects head and trunk. The *trunk* [truncu includes *thorax*, *abdomen*, and *pelvis*. The *upper extremity* [extremitas superio includes *arm* [brachium], *forearm* [antibrachium], and *hand* [manus]. Th *lower extremity* [extremitas inferior] includes *thigh* [femur], *leg* [crus], and *fo* [pes].

Each of the parts mentioned has further subdivisions, as indicated in **fig.** The cranium includes: *crown* [vertex]; *back* of the head [occiput]; *frontal* regio [sinciput], including *forehead* [frons]; *temples* [tempora]; *ears* [aures], includin *auricles* [auriculæ].

The face includes the regions of the *eye* [oculus], *nose* [nasus], and *mouth* [os], the subdivisions of which will be given later under the appropriate sections.

The thorax includes: *breast* [pectus]; *mammary gland* [mamma]; and *thoracic cavity* [cavum thoracis]. The *back* [dorsum] includes the vertebral column [columna vertebralis]. The abdomen includes: *navel* [umbilicus]; *flank* [latus]; *groin* [inguen]; *loin* [lumbus]; and the *abdominal cavity* [cavum abdominis]. The pelvis includes: *pelvic cavity* [cavum pelvis]; *genital organs* [organa genitalia], *buttocks* [nates], separated by a cleft [crena ani] at the *anus*. The *hip* [coxa] connects the pelvis with lower extremity.

Fig. 1.—Parts of the Human Body. A, Posterior view. B, Anterior view.



In the lower extremity, the thigh is joined to the leg by the *knee* [genu]. The foot includes: *heel* [calx]; *sole* [planta]; *instep* [tarsus]; *metatarsus*; and five *toes* [digiti I–V], including the *great toe* [hallux] and *little toe* [digitus minimus].

The upper extremity is joined to the thorax by the *shoulder*. The arm i joined to the forearm at the *elbow* [cubitus]. The hand includes: *wrist* [carpus] *metacarpus*, with *palm* [vola or palma] and *back* [dorsum manus]. The fiv *fingers* [digiti I–V] include: *thumb* [pollex], *index* finger [index]; *middle* finge [digitus medius] *ring* finger [digitus annularis] and *little* finger [digitus minimus].

Organ-systems.—Each of the various parts of the body above outlined i composed of various *organs*, and the groups of related organs make up *organ-systems*.

The various organ-systems are treated as special branches of descriptiv anatomy. The study of the *bones* is called *osteology;* of the *ligaments* and *joints* *syndesmology* (or arthrology); of the *vessels, angiology;* of the *muscles, myology;* o the *nervous system, neurology;* and of the *viscera, splanchnology*. Further subdivisions are also made. The viscera, for example, include the *digestive* tract, *respiratory* tract, *urogenital* tract, etc.

Tissues and cells.—The body, as above stated, has various parts, each of which may b subdivided into its component systems and organs. A further analysis reveals a continued series of structural units of gradually decreasing complexity. Thus each organ is found to consist of a number of *tissues* (epithelial, connective, muscular or nervous). Finally, each tissue is composed of a group of similar units called *cells* which are the ultimate structural units o the body. The body may therefore be regarded as composed of myriads of cell units, organized into units of gradually increasing complexity, very much as a social community is composed of individuals organized into trades, municipalities, etc.

Most of the individual tissues can be recognized by their gross appearance. In fact, the principal tissues were first demonstrated by Bichat through skilful dissection, maceration, etc., and without the aid of the microscope. The cellular structure of the tissues was later discovered by Schwann in 1839.

Each cell is composed of a material called *protoplasm*, a viscid substance variable in appearance and exceedingly complex in chemical composition. It readily breaks down into simpler chemical compounds, whereby energy (chiefly in the form of heat and mechanical energy) is liberated. It has also the power of absorbing nutritive material to build up and replace what was lost. Its decomposition results from stimuli of various kinds, and hence it is said to be irritable. The mechanical energy which it liberates is manifested by its contractility, especially in the muscle cells. It excretes the waste products produced by its decomposition. Each cell has the power, under favorable conditions, of reproducing itself by division. Protoplasm presents, in short, all the forms of activity manifested by the body as a whole; and indeed, the activities of the body are the sum of the activities of its constituent cells.

In the protoplasm of each cell is a specially differentiated portion, the *nucleus*. The nucleus plays an important part in regulating the activities of the *cytoplasm*, the general protoplasm of the cell body. The nucleus differs from the cytoplasm both structurally and chemically, and contains a very important substance, *chromatin*, which during cell division is aggregated into a definite number of masses called *chromosomes*. Further details concerning the cells and tissues may be found in the text-books of cytology and histology.

In earlier days human anatomy was almost entirely a descriptive science, but little attention being paid to the significance of structure, except in so far as it could be correlated with physiological phenomena as they were at the time understood. In recent years attention has been largely paid to the morphology of the human body and much valuable information as to the meaning of the structure and relations of the various organs has resulted. Since the form and structure of the body are the final result of a series of complicated developmental changes, the science of embryology has greatly contributed to our present knowledge of human morphology, and, accordingly, an account of some of the more important phases of morphogenesis and developmental anatomy will form a fitting introduction to the study of the adult.

References.—*General:* For looking up the literature upon any anatomical topic, the best guide in general is the Jahresbericht über die Fortschritte der Anatomie und Entwicklungsgeschichte, which contains classified titles and brief abstracts of the more important papers in gross anatomy, histology and embryology. Other useful aids are the Index Medicus and the catalogue of the Surgeon General's Library of the War Dep't. (Washington, D. C.). The latter two contain titles only, but cover the whole field of medicine. The Concilium Bibliographicum also provides a convenient card-index system of references for the biological sciences, including Anatomy. For *nomenclature:* His, Archiv f. Anat., 1895 (BNA system); Barker, Anatomical Nomenclature; Eycleshymer, Anatomical Names. *Cells and tissues:* Wilson, The Cell; Hertwig, Zelle und Gewebe (also English transl.); Schaefer, Microscopic Anatomy (in Quain's Anatomy, 11th ed.); Heidenhain, Plasma und Zelle; Kölliker, Gewebelehre; Prenant, Bouin et Maillard, Traité d'Histologie.

SECTION I

DEVELOPMENTAL ANATOMY

REWRITTEN FOR THE SIXTH EDITION

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THE life history of man, in common with most higher organisms, is characterized by continuous change and presents a cycle in which may be recognized the succeeding phases of growth and differentiation, maturity, and old age or senescence. In man nearly one-third of the traditional span of life is required for the body to reach its full size and differentiation. This portion of the human life cycle may be called the developmental period, and the study of the structure of the body and its changes in this time may be termed developmental anatomy.

Divisions of the developmental period.—The developmental period is divided by the incident of birth into prenatal and postnatal epochs and in these a number of more or less arbitrarily defined subdivisions may be recognized. The divisions of the developmental period are shown on the following table. In this scheme puberty is regarded only as a transition point between later childhood and adolescence. The length of the developmental period and of its several subdivisions varies greatly with sex, race, environment, and physical constitution. A distinction is often drawn between the anatomic or physiologic age of the individual, as indicated by the degree of physical development of the body, and the calendar or chronologic age. As females pass through most of the transitions of the developmental period a little earlier than do males the physiologic age of girls is usually somewhat greater than that of boys of the same calendar age.

DIVISIONS OF THE DEVELOPMENTAL PERIOD IN MAN

- **Prenatal life**
  - *Period of the ovum.*
    From fertilization to the close of the second week of prenatal life.
  - *Period of the embryo.*
    From the close of the second week to the close of the second (lunar) month.
  - *Period of the fetus.*
    From the close of the second (lunar) month to birth at 10 lunar months.

Birth

- **Postnatal life**
  - *Period of the newborn* (Neonatal period).
    From birth to the close of the second (postnatal) week.
  - *Infancy.*
    From 2 weeks to the close of the first year or until the habitual assumption of the erect posture (usually in the thirteenth or fourteenth month).
  - *Childhood*
    - *Early childhood* (Milk-tooth period).
      From 1 to 6 years.
    - *Middle childhood.*
      From 6 to 9 or 10 years.
    - *Later childhood* (Prepuberal period).
      From 9 or 10 years to 12–15 years in females and 13–16 years in males.
  - *Puberty*
    Fourteenth year in females. Sixteenth year in males. (According to American data.)
  - *Adolescence.*
    From puberty to the last years of the second decade in females and to the first years of the third decade in males.

Growth and differentiation.—The changes which characterize the developmental period do not take place at the same time or at equal rates in all regions of the body, for each organ and part has its own peculiar life cycle. In a few organs, such as the mesonephros of the embryo, this cycle is very short. Other organs persist during childhood and then decline, while the great majority continue, with varying degrees of change, throughout postnatal life.

The characteristic life cycle of the various organs depends upon the changes in the structural units which compose them and, in the last analysis, upon the growth and differentiation of their constituent cells. Each cell has a definite life cycle, an early period of rapid and vigorous changes, later periods of differentiation and maturity, followed by stages of degeneration and death. This cycle of cell changes is termed *cytomorphosis*. The length of life cycle of the various types of cells in the body differs greatly, some of the blood cells living probably a month or less while certain brain cells may survive throughout postnatal life. The growth of cells may take place either by the enlargement (hypertrophy) of individual cells or by the multiplication (hyperplasia) of cells by mitosis. Cell division is necessary for continued cell growth for otherwise the cell would soon reach a size where its surface would be inadequate (for nutritive, respiratory and excretory purposes) to its mass. In general, however, cell division is most active in the early embryonic periods, during which the cells remain small. Later, cell division diminishes or ceases, and growth is due chiefly to the enlargement of cells already present. The growth of the structural units of organs also follows this general rule, the production of new units being confined mainly to fetal and early postnatal life.

While the functional and structural differentiation of cells and structural units may take place during the period of their rapid multiplication these processes are usually partially disassociated and the phase of active differentiation comes some time after the period of most active growth.

THE EARLY DEVELOPMENT OF THE EMBRYO

The germ-cells and fertilization.—The period of development in man, as in the great majority of multicellular animals, is inaugurated by the process of fertilization which consists of the union of the male germ-cell or spermatozoon with the female germ-cell or ovum.

The ovum and spermatozoon are differentiated, by the process of maturation, from certain more primitive germ-cells set aside from the general body or somatic cells at an early period in development. In maturation both the ovum and spermatozoon undergo profound nuclear changes and each becomes highly specialized in form and structure for its part in the fertilization process.

The ripe spermatozoon or sperm is a slender lance-like structure 0.05 or 0.06 mm. long (fig. 3).

The ripe human ovum or egg-cell is a spheroidal body whose greatest diameter is approximately 0.1 mm. (fig. 2). It contains a nucleus about 0.02 mm. in diameter which is generally slightly eccentric in position. Suspended in the protoplasm of the cell-body are numerous droplets and granules which are presumably reserve food substances. The ovum is bounded by a delicate vitelline membrane.

Fertilization has not been observed in man but it has been studied in detail in several mammals and it is most probable that the process is essentially the same in all higher forms. After escaping from the ovary through the rupture of the Graafian follicle the ovum enters the ostium of the uterine tube and passes down the lumen. The union of the ovum with the spermatozoon probably takes place in most cases during this process.

Segmentation of the ovum.—The fertilized ovum is converted into a solid ball of much smaller cells by a series of cell-divisions. This process is known as segmentation and the mass of cells resulting from it is called the *morula*. Like fertilization, segmentation has not been observed in man and our concepts of the process in the human species are based upon observations on the ova of lower animals. It is probable that the first segmentation divisions are equal but that the later ones are quite irregular. The morula which results from them is a solid body at first but an eccentrically placed cavity soon appears within it and the structure is differentiated into an outer shell, the *trophoblast*, and a cluster of cells termed the *inner cell-mass*. The inner cell-mass is broadly attached to the inner surface of the trophoblast and the cavity between the two is filled with fluid and bridged by delicate cellular strands, the *magma reticulare*.

It is probable that after fertilization approximately ten days are required for the ovum to reach this stage of development. During this period the ovum has left the uterine tube and has come to rest on the inner surface of the uterus. The uterine epithelium in contact with the ovum is destroyed, presumably

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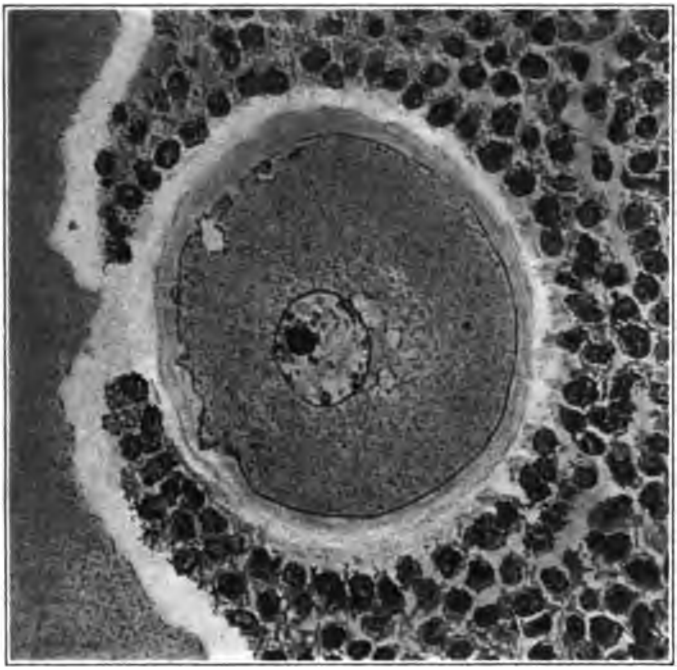
through the activity of the cells of the trophoblast, and the ovum sinks into the uterine mucosa and is inclosed by it. Until this implantation takes place the ovum is an independent organism dependent upon its own scanty reserve food supply for nourishment. Consequently it grows little if any during this period. With implantation, however, the ovum becomes, in a fashion, a parasite upon the maternal organism from which it derives its nourishment throughout the remainder of the fetal period. With the establishment of this relation the ovum enters on a period of extremely rapid growth.

Fig. 2.—Mature Ovum, with Follicular Cells, of a Woman 36 Years Old. (After Thompson.) ×500.



Formation of the embryonic disk.—Two spaces now appear in the inner cell-mass, an upper one, the amniotic cavity and a lower one, the yolk-sac cavity. These are separated by a plate of cells, the *embryonic disk*. At the same time a distinct layer of cells is differentiated on the outer surface of the cell-mass. This layer is the extraembryonic mesoderm. It is probably formed in part from the cells of the inner cell-mass and the trophoblast and in part from the magma reticulare. The extraembryonic mesoderm forms a complete lining about the original cavity of the morula and this space is now termed the *extraembryonic celom*. As the extraembryonic celom is established the magma reticulare disappears and the connection between the inner cell-mass and the trophoblast is reduced to a short bridge of extraembryonic mesoderm, the connecting stalk (fig. 4).

Fig. 3.—Mature Spermatozoa.

A, frontal view showing broad surface of the head: B, anterior portion in side view. (After Broman.) ×2500.

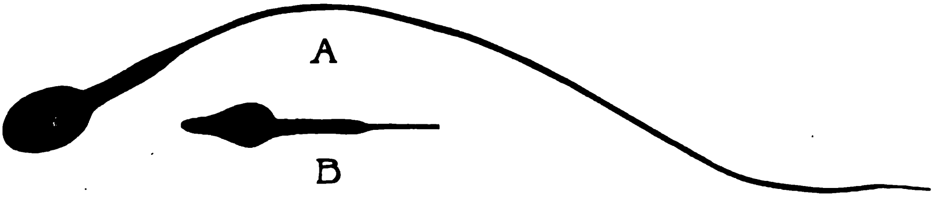
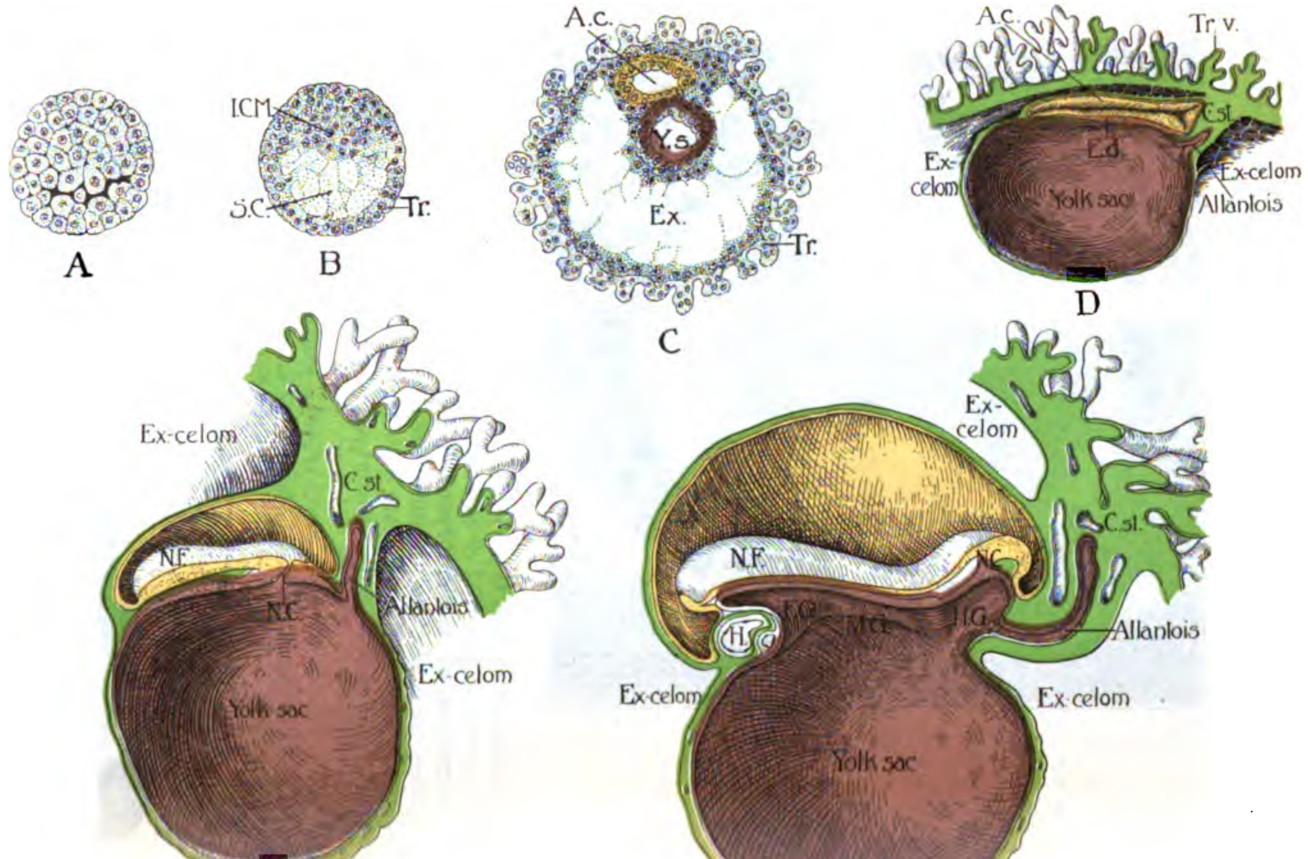


FIG. 4.—A SERIES OF DIAGRAMS ILLUSTRATING THE LATER CHANGES IN THE OVUM AND THE FORMATION OF THE EMBRYO. (Based on the figures of Broman, Brödel, Dandy, Eternod, Lewis, Miller and Streete.)

A, morula (hypothetical). B, differentiation of the inner cell-mass and trophoblast (hypothetical). C, formation of the amniotic cavity, yolk-sac and extraembryonic celom. D, formation of the embryonic disk. E and F, formation of the archenteron and neural canal. A.c., amniotic cavity. C.st., connecting stalk. E.d., embryonic disk. Ex., extraembryonic celom. F.G., foregut. H., heart. H.G., hindgut. I.C.M., inner cell-mass. N.C., neurenteric canal. N.F., neural folds. S.C., segmentation-cavity. Tr., trophoblast. Tr.v., trophoblastic villi. Y.s., yolk-sac.

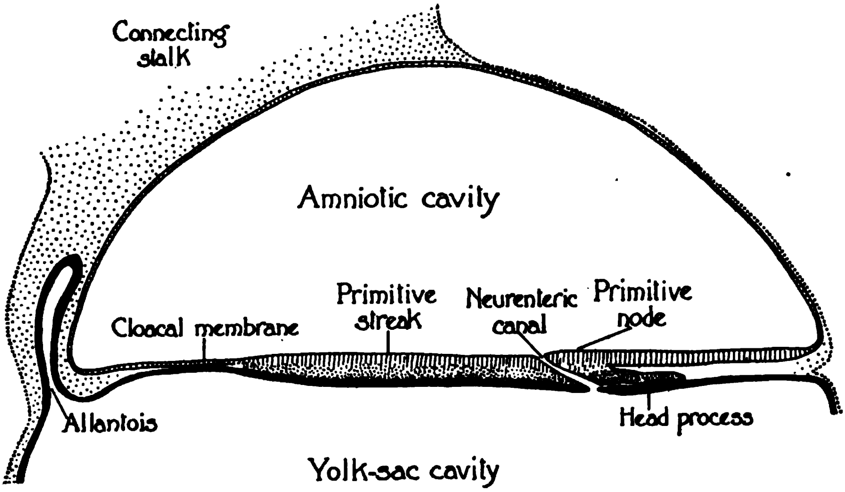


Our interest is centered in the embryonic disk, for the embryo is entirely a product of this structure: the remainder of the ovum gives rise to the supporting or nourishing structures for the developing embryo or else disappears comparatively early in prenatal life.

The embryonic disk in embryos of the third week is an oval plate having a maximum diameter of about 0.2 mm. It consists of three sheets of cells called the germ layers. The upper layer or ectoderm forms the floor of the amniotic cavity and becomes continuous with the walls of the amnion at the margins of the embryonic disk. The lower layer or entoderm forms the roof of the yolk-sac and is continued as the walls of this structure at the periphery of the embryonic disk. The middle layer or mesoderm forms an incomplete plate between the ectoderm and entoderm. At the margins of the embryonic disk it becomes continuous with the extraembryonic mesoderm which covers the outer surface of the inner cell-mass.

The subsequent history of the embryo is essentially that of the differentiation and the disposition of the germ-layers. Their contributions to the adult body are as follows:

FIG. 5.—DIAGRAM OF A LONGITUDINAL SECTION THROUGH THE LONG AXIS OF THE EMBRYONIC DISK AT THE TIME OF FORMATION OF THE PRIMITIVE STREAK AND NEURENTERIC CANAL. (Based in part on the figures of Ingalls and Streeter.)



From the ectoderm are formed:

The central and peripheral nervous system, the epithelial internal ear, the lens, iris and retina of the eye. The epithelial portion of the skin and its appendages.

The lining of the buccal, nasal, and a part of the pharyngeal cavities; the enamel of the teeth; the salivary glands.

The lining of the anal canal; the lining of the vestibule and a portion of the urethra in the male, with associated glands.

The anterior lobe of the hypophysis cerebri; the pharyngeal hypophysis. The paraganglia.

From the entoderm are formed:

The lining epithelium of the digestive tract, with the exception of the mouth, a part of the pharynx, and the anal canal; the parenchyma of the digestive glands, pancreas and liver. The lining of the larynx, trachea, bronchi and lungs.

The lining of a portion of the bladder; the lining of the female urethra and a part of the male urethra, with associated glands.

The parenchyma of the thyroid and parathyroid glands; the reticulum and the thymic corpuscles of the thymus.

From the mesoderm are formed:

The skeletal and muscular structures and the connective tissues of the body.

The vascular system; the lymphoid and sanguifactive organs.

The serous membranes.

The genital glands and their ducts and accessory structures. The kidneys, ureters and the greater part of the bladder.

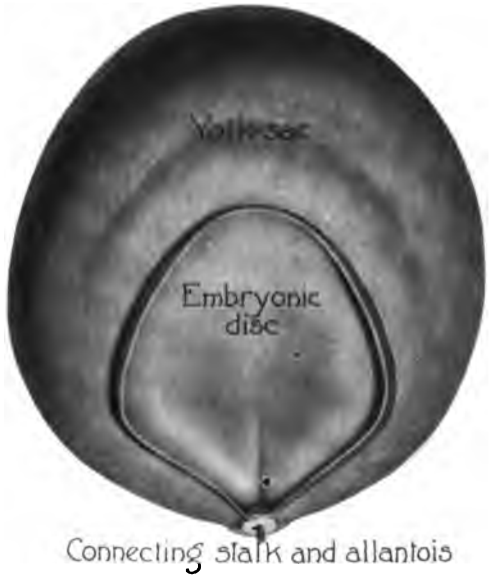
The dentine and cementum of the teeth.

The cortex of the suprarenal glands.

Early changes in the embryonic disk.—The first indications of the establishment of the embryo on the germinal disk appear early in the third week. At this time the ectoderm and entoderm in the posterior part of the longitudinal axis of the disk fuse forming a band of cells known as the primitive streak. The primitive streak is indented by a dorsal primitive groove (fig. 6). It terminates anteriorly in an enlargement, the primitive node, and from the node a mass of cells, the head-process, extends forward in the midline, fusing below with the entoderm of the yolk-sac in this region. A narrow channel, the neurenteric canal, pierces the primitive node and connects the amniotic cavity with the yolk-sac cavity. The neurenteric canal is continuous with a cleft in the head-process termed the head-process canal (fig. 5). As these changes take place on the germinal disk a small tubular outgrowth, the allantois, arises from the posterior end of the roof of the yolk-sac and grows upward, behind the amnion, into the connecting-stalk.

The primitive groove, the primitive streak, the primitive node, neurenteric canal, and head-process are ephemeral structures which may be regarded as representing a highly modified process of gastrulation in the human embryo. The primitive streak and node and the head-process join the mesoderm laterally and presumably contribute cells to this germ-layer. The head-process also gives rise to a longitudinal rod of cells, the notochord, which forms the median longitudinal axis of the embryo and is subsequently associated with the skeleton; possibly its ventral part is incorporated in the entoderm of the yolk-sac. With this distribution of its material the head-process disappears as a separate structure. The primitive streak becomes relatively shorter with the growth of the embryo anterior to it and the consequent migration backward of the primitive node. After the third week it is no longer recognizable. The neurenteric canal is normally obliterated in the third week.

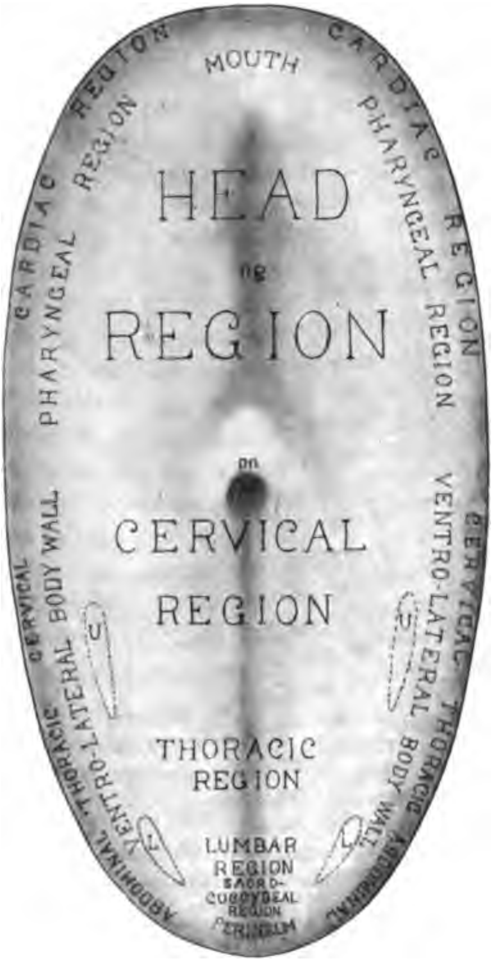
FIG. 6.—DORSAL VIEW OF THE EMBRYONIC DISK AND YOLK-SAC OF AN EMBRYO OF THE EARLY PART OF THE THIRD WEEK. (After Streeter.)



The topography of the embryonic disk.—Although only slight signs of differentiation are visible on the surface of the embryonic disk in the third week it is possible to map out upon it more or less definite areas corresponding to all of the various regions of the future body, as shown in fig. 7. Beginning anteriorly, the head region is relatively enormous in size, occupying the entire area in front of the primitive node and forming about half of the entire disk. The cervical, thoracic, lumbar, and sacrococcygeal regions appear successively smaller, approaching the posterior end ('tail-bud') of the primitive streak. It is also a striking fact that the future dorsal region of the body wall, corresponding to the central portion of the disk, along each side of the midline, is now larger than the ventrolateral regions, which occupy a relatively narrow zone around the periphery of the disk.

Early changes in the germ layers.—The definitive embryo is formed by the rapid growth of the dorsal region of the embryonic disk and by a series of folds and cleavages of the germ-layers of this area. The **ectoderm** plays a most active part in these early transformations. Shortly after the primitive streak is established, the ectoderm along the midline of the embryonic disk is thickened into a neural plate which extends from the primitive node to the anterior end of the disk. The lateral margins of the plate grow rapidly and rise from the surface of the disk as a pair of longitudinal neural folds or ridges which bound a shallow neural groove (figs. 8 and 12*A*). The neural plate is converted into the *neural tube* by the further growth of the neural ridges which fold over the neural groove and fuse in the midline. This process begins in the future cervical region and extends forward and backward from this level (fig. 12*A*). The extreme anterior and posterior ends of the tube remain open for a time as the anterior and posterior neuropores. With their subsequent closure the walls of the tube are completed and its cavity is entirely separated from the amniotic cavity. The neural tube gives rise to the brain, spinal cord, and retinæ and optic nerves. Its further history is considered in connection with the nervous system.

FIG. 7.—TOPOGRAPHY OF THE EMBRYONIC DISK. Diagram of relations at the length of about 1 mm. ng, neural groove. pn, primitive node. pp, primitive pit. U, upper limb. L, lower limb.

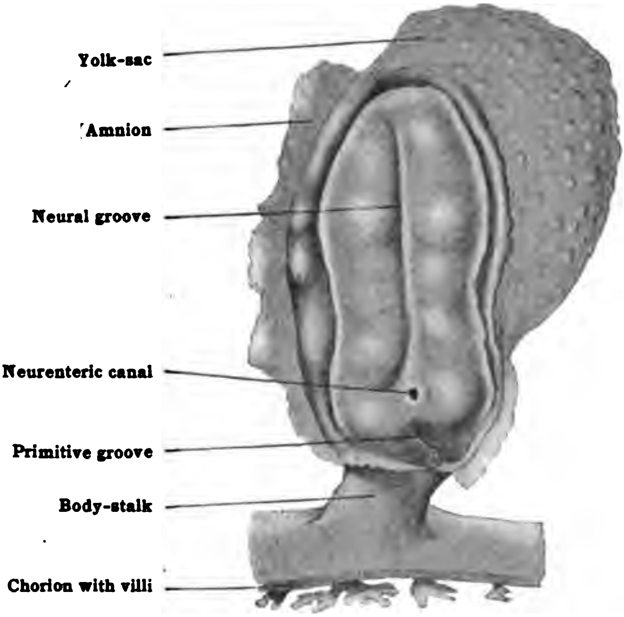


The ectoderm which covers the periphery of the embryonic disk is carried over the dorsal surface of the neural tube with the infolding of the neural ridges. It forms the external covering of the embryo.

The entoderm.—As the neural plate is formed from the ectoderm on the upper surface of the embryonic disk, the entoderm lying below this region is folded into the primitive digestive tube or *archenteron*. In embryos of the latter part of the third week three divisions, the *foregut*, the *hindgut*, and the *midgut* may be recognized in this structure (figs. 4*E*, 4*F*). The midgut is a shallow groove still broadly connected with the yolk-sac, the foregut is a pocket-like projection from the midgut extending forward under the anterior part of the neural plate, and the hindgut is a similar but shorter projection which extends into the caudal region of the developing embryo.

With the further growth of the archenteron the foregut and hindgut become considerably elongated and the connection of the midgut with the yolk-sac is reduced to a short, wide yolk-stalk. In this process the upper part of the posterior wall of the yolk-sac is incorporated in the floor of the hindgut, and the allantois now takes origin from this part of the archenteron instead of the yolk-sac. The later history of the entoderm will be considered in connection with the development of the digestive and respiratory tracts.

FIG. 8.—HUMAN EMBRYO 1.54 MM. LONG. Viewed from above, the roof of the amniotic cavity having been removed. (Minot, after Graf Spee.)



The mesoderm.—The mesoderm of the human embryo appears to have a dual origin being formed primarily from the extraembryonic mesoderm of the inner cell-mass and secondarily from the primitive streak, primitive node, and head-process. After the formation of the notochord the mesoderm takes the form of a pair of plates which lie on either side of the longitudinal embryonic axis and which are continuous laterally with the extraembryonic mesoderm covering the amnion and yolk-sac. Behind the primitive node these plates fuse with the primitive streak across the midline of the embryonic disk but anterior to the node they are separated by a medial space which contains the notochord (figs. 9, 10.)

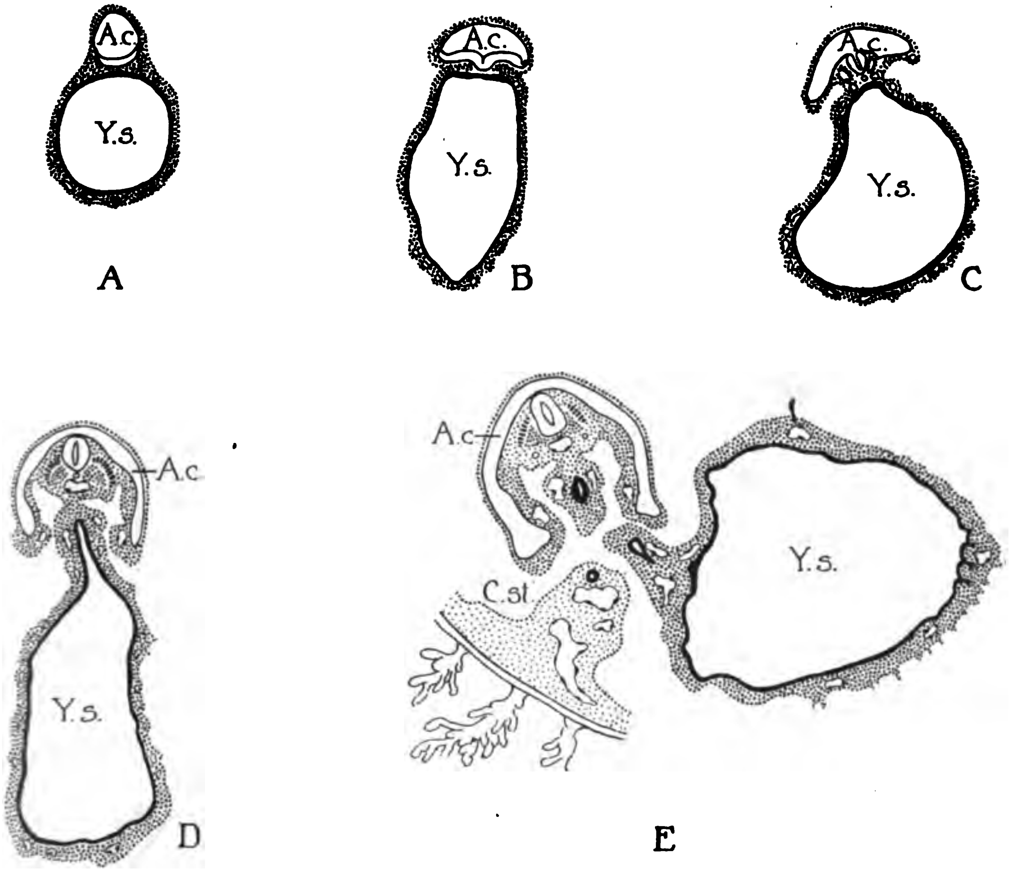
Some of the later changes in the mesoderm are shown in fig. 10. Each plate of mesoderm is divided by a longitudinal groove into three parts. These are (1) a narrow medial strip, the medial or paraxial mesoderm, (2) the intermediate mesoderm which forms a slender cord lying beneath the longitudinal groove, and (3) a broad band of lateral mesoderm. The *medial mesoderm* is subdivided by a series of transverse clefts into a row of blocks or segments known as the *mesodermic somites.* At the same time the lateral mesoderm splits into an upper (outer) or somatic layer and a lower (inner) or splanchnic layer. The space between these two layers is the embryonic body cavity or *celom.* It becomes continuous with the extraembryonic celom at the lateral margins of the embryonic disk.

The appearance of the mesodermic somites marks the beginning of metamerism, the arrangement of the body in successive segments or metameres. The somites form first in the occipital region and rapidly differentiate in the craniocaudal direction. In embryos 7 or 8 mm. in length about 40 pairs of somites can be distinguished.

The anterior end of the *medial mesoderm*, which is continued into the head region, does not undergo segmentation in the human embryo. From it are formed the cranial bones, certain of the muscles of the head and connective tissue.

FIG. 9.—CROSS-SECTIONS OF A SERIES OF YOUNG HUMAN EMBRYOS. All drawn at the same magnification. (Slightly modified from Graf Spee.)

A, embryo of the middle of the third week. B, embryo of the end of the third week. C, embryo of the early part of the fourth week. D, embryo of the latter part of the fourth week. E, embryo of the fifth week. A.c., amniotic cavity. C.st., connecting stalk. Y.s., yolk-sac. The mesoderm is indicated in stipple.

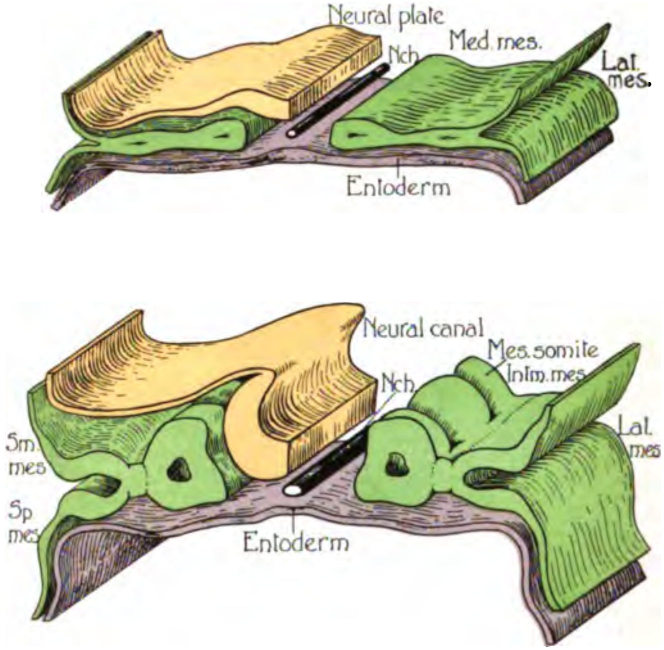


A small cavity, the *myocele* appears in the center of each somite and the wall separates into an upper lateral part, the *dermomyotome*, and a lower medial part, the *sclerotome*. From the dermomyotomes are formed the voluntary muscles of the trunk, neck, and a part of the head; while the sclerotomes take part in the development of the axial skeleton. Probably both parts of the somite contribute cells to the mesenchyma which forms the connective tissue of the body wall, and the supporting structures and voluntary muscles of the limbs.

The greater part of the *intermediate mesoderm* is also divided into segments or *nephrotomes* (corresponding to the somites), portions of which form the transitory uropoietic organs, the pronephros and mesonephros. The posterior part of the intermediate mesoderm remains unsegmented as the nephrogenic cord which is later involved in the development of the permanent kidney.

The *lateral mesoderm* shows no evidences of segmentation. The lateral cavities which are formed between its upper and lower layers soon lose their connection with the extraembryonic body cavity and fuse in the midline, forming the general celom to be described later.

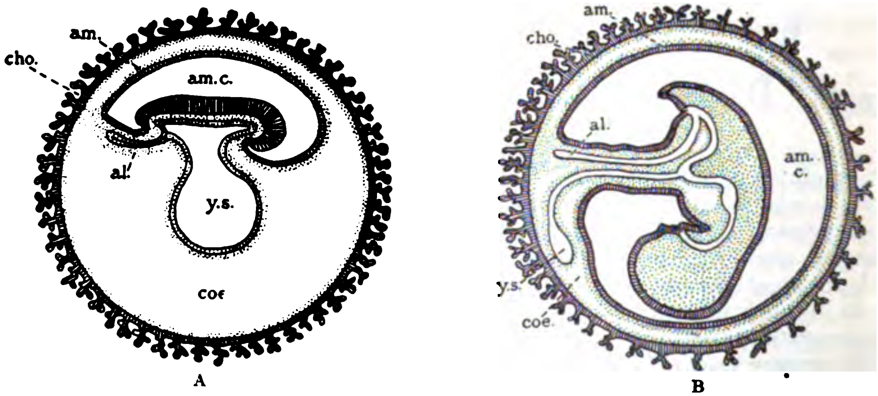
Fig. 10.—Stereograms Illustrating the Early Changes in the Mesoderm. Intm.mes., intermediate mesoderm. Lat.mes., lateral mesoderm. Nch., notochord. Sm.mes., somatic layer of lateral mesoderm. Sp.mes., splanchnic layer of lateral mesoderm. Ectoderm, yellow; mesoderm, green; entoderm, red.



THE DEVELOPMENT OF THE EXTERNAL BODY-FORM

The early transformations of the germ-layers convert the embryonic disk into a cylindrical structure which is only partially connected with yolk-sac and connecting stalk (fig. 11). The cylindrical body wall now encloses two tubes (neural and enteric) with a longitudinal axis (notochord) between them, and is covered by an outer layer of skin-ectoderm which is continuous along the sides of the embryo with the ectoderm of the amnion. The head is relatively large and is separated from the disk below it by a deep head fold. The caudal end

Fig. 11.—Diagrams Illustrating the Development of the Embryonic Membranes and the Formation of the Umbilical Cord. (After Lewis.) al., allantois. am., amnion. am.c., amniotic cavity. cho., chorion. coe., celom. Y.s., yolk-sac.



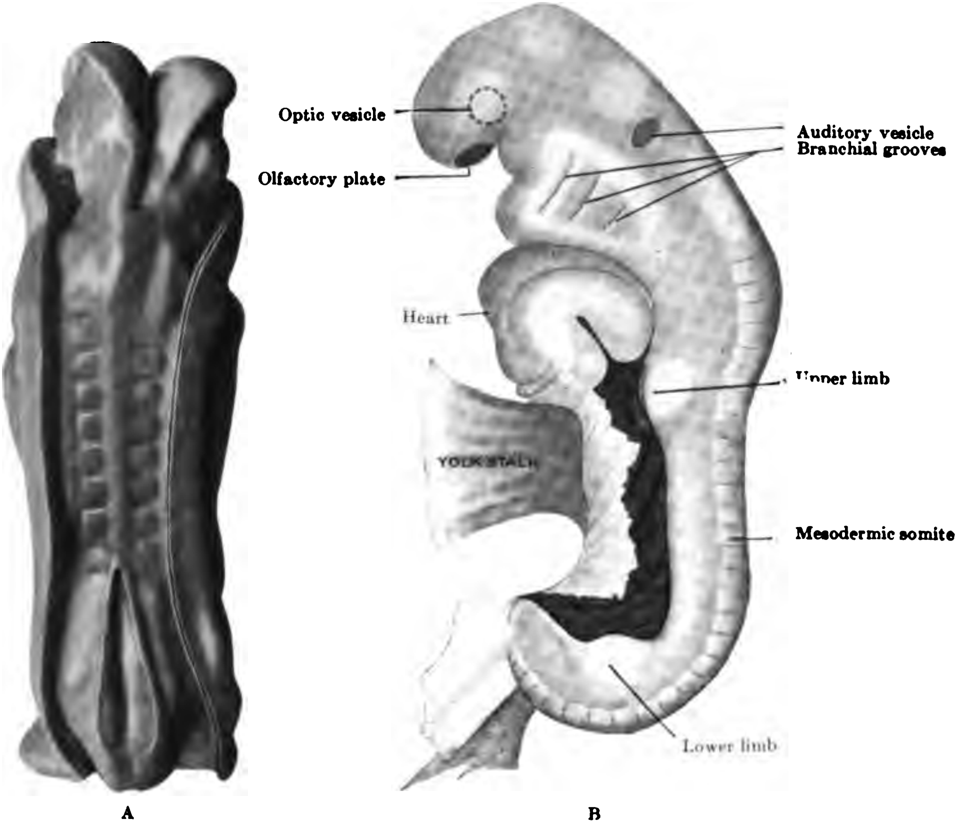
A

B

of the embryo is prolonged into a short tail-bud which is also marked off from the disk by a shallow tail-fold. The middle portion or trunk is still widely connected with the disk, but its boundaries are indicated by distinct lateral folds.

The embryo becomes further separated from the other structures derived from the inner cell-mass by the deepening of the head, tail, and lateral folds; and its connection with these structures is reduced to a slender *umbilical cord.* This cord contains the allantois and yolk-stalk (with their surrounding mesoderm) and is covered by the ectoderm which is reflected from the amnion upon the external surface of the embryo.

FIG. 12.—A, HUMAN EMBRYO 2.11 MM. LONG. (FROM A MODEL BY ETERNOD.) B, HUMAN EMBRYO 4.2 MM. LONG, SHOWING THREE BRANCHIAL GROOVES. (After His.)



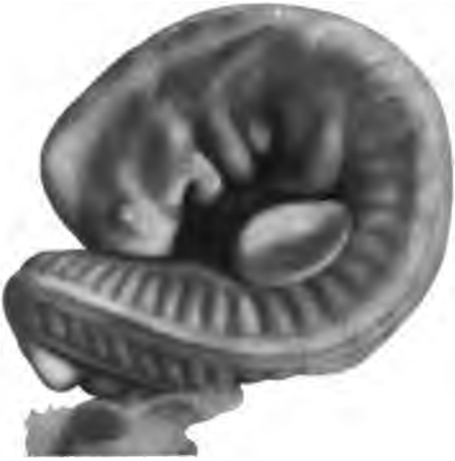
Coincident with these changes, the longitudinal axis of the embryo is modified by the formation of a series of flexures or bends. The head is flexed on the trunk first by an anterior cephalic flexure, and soon after by a more posterior cervical flexure, and the caudal part of the trunk and the tail are bent downward in a semicircular curve (fig. 12B). Later the rapid growth of the dorsal region throws the entire body into a partial spiral (coiled either to the right or left) so that its outline, when seen in lateral view, may be almost circular (fig. 13).

The ventral part of the body increases in size very rapidly in the second fetel month through the great growth of the contained viscera. With this growth the axis of the trunk is straightened and the cervical flexure partially eliminated The cephalic and caudal flexures are never completely obliterated, although the latter is obscured by the growth of the lower limbs; and the external evidences of the former are masked by the subsequent changes in the proportions of the head and face.

A well marked tail appears which in embryos 7 to 8 mm. long may be nearly one-sixth as long as the body. Regression of the tail structure begins in the sixth week and by the ninth week it has usually entirely disappeared.

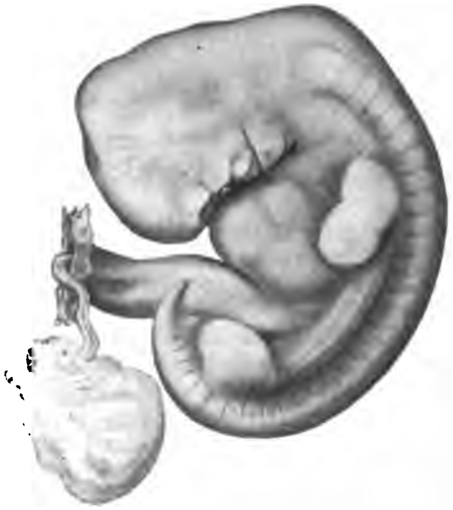
Deveploment of the head and neck.—The head is divisible from an early stage, into a neural portion including the brain, eyes and internal ears with their supporting structures, and a facial or visceral part which contains the anterior termination of the digestive-respiratory tract. The growth and differentiation of these two portions are quite dissimilar. The neural portion is by far the larger in the young embryo and this predominance is never completely lost although it is greatly reduced during both fetal and postnatal life by the growth of the accessory structures of the mouth, nose and pharynx.

FIG. 13.—HUMAN EMBRYO 4.02 MM. LONG. (After Hochstetter.)



In the fourth and fifth weeks the visceral portion of the head undergoes marked external changes. A median *oral sinus* or embryonic mouth is formed on the ventral surface, and anterior to the sinus a pair of small *nasal pits*. The nasal pits are bounded laterally by lateral nasal processes; and a broad medial process separates them and extends downward forming the middle part of the upper boundary of the oral sinus. The remainder of the margin of the oral sinus is formed from the mandibular and maxillary processes of the first branchial arch, the maxillary processes forming the lateral thirds of the upper boundary and he mandibular processes the entire lower margin. The maxillary and medial nasal processes are separated for the time by shallow lacrimal grooves (figs. 13, 14 and 17).

FIG. 14.—HUMAN EMBRYO 11.5 MM. LONG. (After Minot.)



The margins of the sinus are completed by the coalescence of the mandibular processes below and the fusion of the maxillary and medial nasal processes above. The definitive *nose* is formed by the fusion of the lateral and medial nasal proc-

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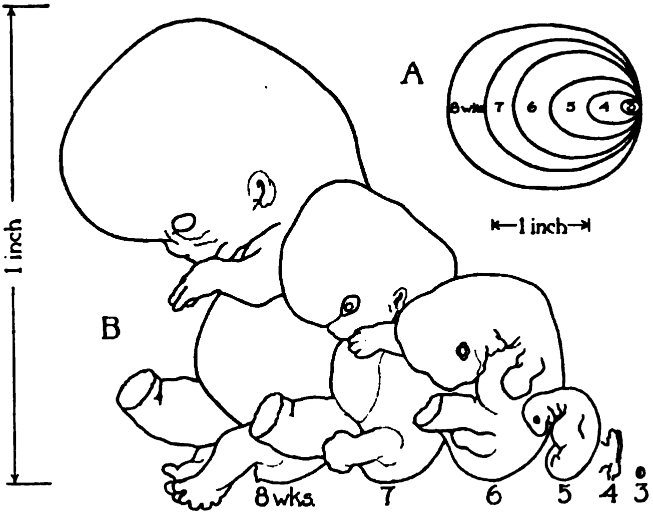
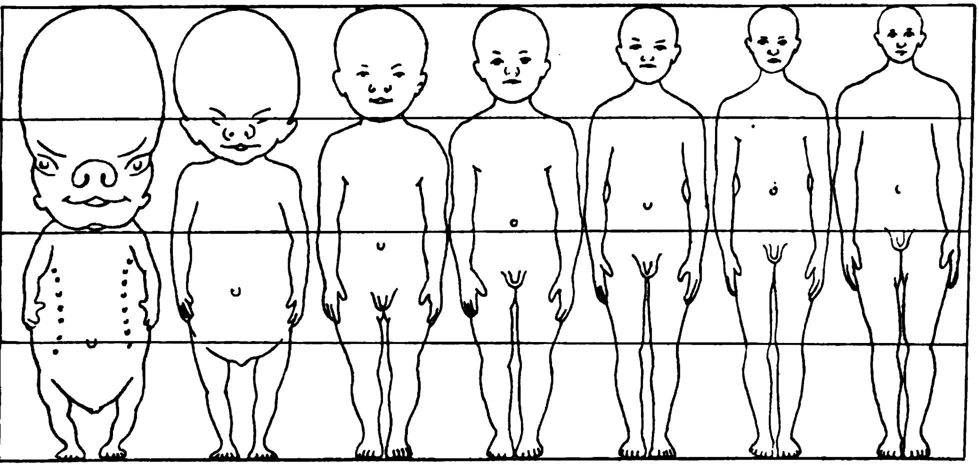
esses at the lower margins of the nasal pits and the subsequent growth of the medial process, particularly in the midline above the nares. The later development of the external features of the face is illustrated by the series of outlines in fig. 18.

FIG. 15.—A, OUTLINES OF AVERAGE HUMAN OVA FROM 3 TO 8 WEEKS OLD, ONE-HALF NATURAL SIZE. B, OUTLINES OF HUMAN EMBRYOS FROM THE THIRD TO THE EIGHTH WEEK, ENLARGED 2.5 TIMES. (After Evans.)



As these changes take place in the facial region the lateral surfaces of the neck are indented by a series of four (paired) *branchial* (visceral) *grooves* which are separated by the *branchial arches*. The upper part of the first of these grooves is deepened to form the *external auditory meatus*, the margins being elevated to form the *auricle*. The region corresponding to the second, third, and fourth grooves becomes depressed, forming the *cervical sinus* which soon closes over and normally disappears.

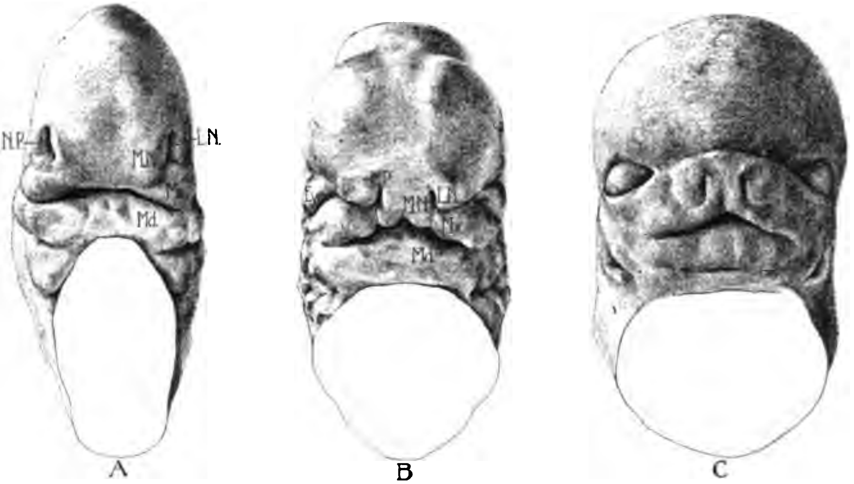
FIG. 16.—FIGURES ILLUSTRATING THE CHANGES IN PROPORTIONS DURING PRENATAL AND POSTNATAL GROWTH. (After Stratz.)



Development of the trunk.—In the young embryo the trunk appears as a cylindrical body flattened from side to side and exhibiting externally the modeling of the viscera contained within it. In fetal life, with the development of the skeleton and trunk musculature and the rounding of the visceral mass, it takes on an ovoid form largest at the level of the umbilicus and almost circular in cross section. In spite of the changes in the form and relative proportions of the contained viscera, the relative proportions of the trunk remain almost unchanged from the close of the third fetal month until birth. In the early part of infancy, also, there is little change in the form of the trunk, but after the assumption of the erect posture there is a reduction of the relative anteroposterior diameter of both the thoracic and abdominal regions accompanied by a decrease in the relative size of the umbilical region and a relative increase in the lumbar region. These changes continue throughout childhood and early adolescence.

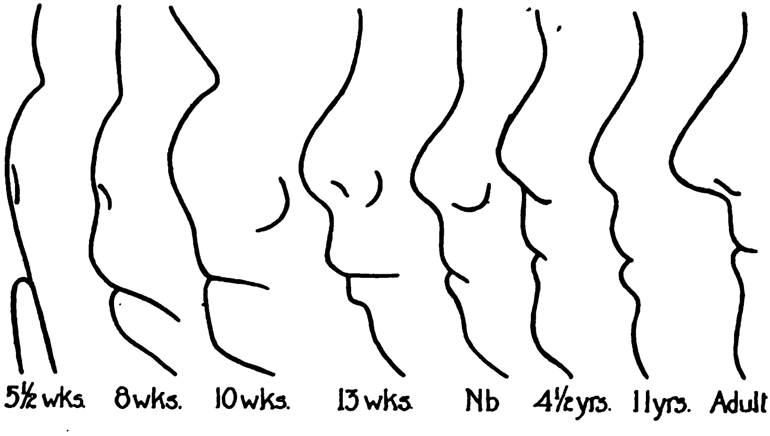
Fig. 17.—Development of the Face in the Second Fetal Month. (From a series of models made in the Department of Embryology of the Carnegie Institution.)

L.N., lateral nasal process. Md., mandibular process. M.N., medial nasal process. N.P., nasal pit. Mx., maxillary process.



Development of the extremities.—The limbs appear about the third week of fetal life as short ridges which project from the lateral surfaces of the cranial and caudal ends of the trunk. Each ridge is differentiated into a limb-bud in which may be recognized a flattened distal segment representing the hand or foot, and a rounded proximal segment representing the remainder of the limb. The latter is again divided by a slight constriction into a distal part, corresponding to the forearm or leg, and a proximal part corresponding to the arm or thigh. The digits are formed as radiating ridges on the lateral surfaces of the hand and foot segments. As these ridges grow more rapidly than the bodies of these segments they soon project beyond their margins as definitive fingers or toes.

Fig. 18.—A Series of Profiles Illustrating the Changes in the Form and Proportions of the Face in the Developmental Period. (After Peter.)



The axes of the limbs undergo three main changes in position in their early development. At first the limb-buds project outward at right angles to the

Fig. 19.—Development of the Upper Extremity. (After Retzius.)

A, anterior limb-bud of an embryo 12 mm. long. B, anterior limb-bud of an embryo 15 m. long. C, anterior limb-bud of an embryo 16 mm. long. D, forearm and hand of an embryo 25 mm. long. E, hand of a fetus 52 mm. long. All ×6.

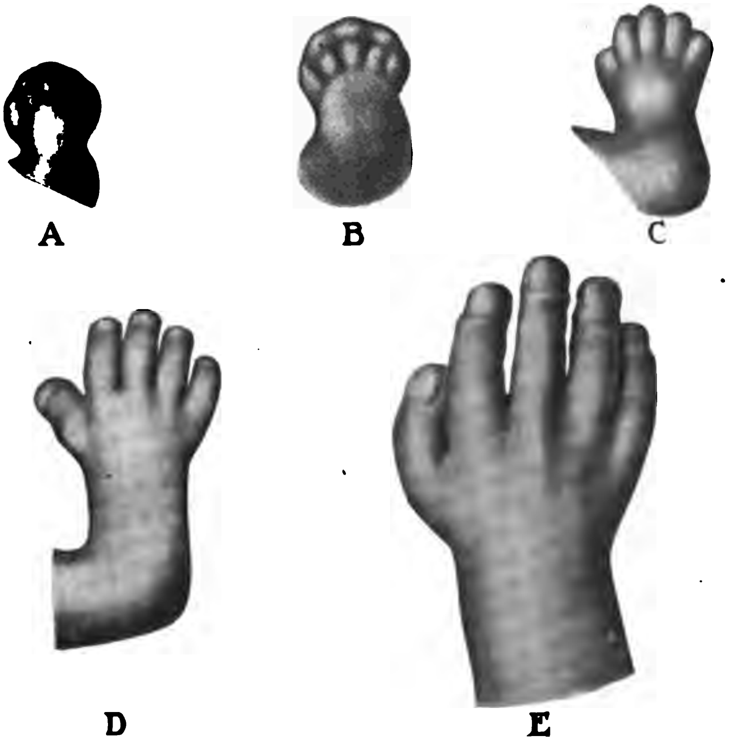
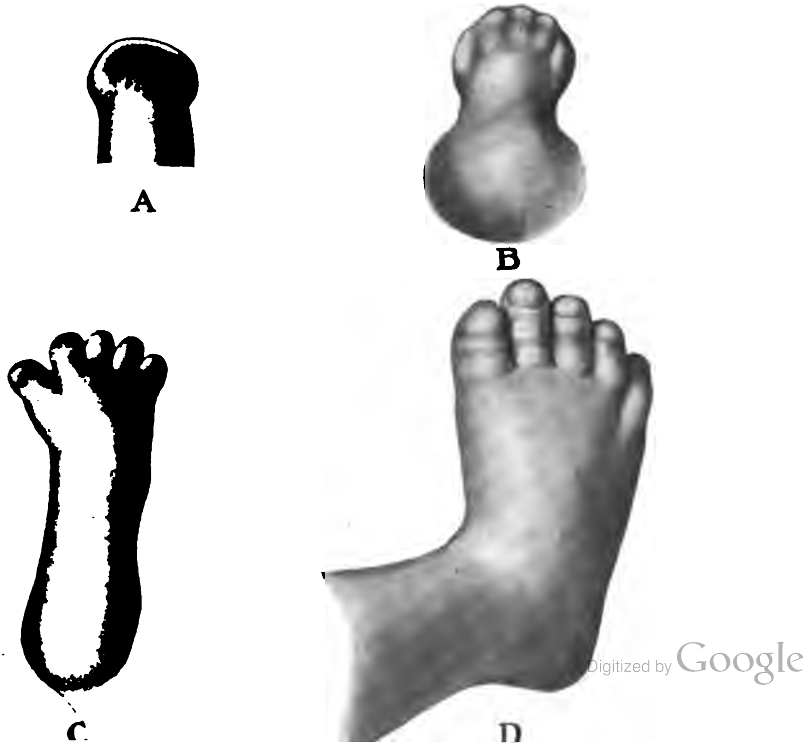


Fig. 20.—Development of the Lower Extremity. (After Retzius.)

A, Posterior limb-bud of an embryo 17 mm. long. B, posterior limb-bud of an embryo 19 nm. long. C, leg and foot of an embryo 25 mm. long. D, foot of a fetus 52 mm. long. All ×6.



lateral surface of the body. Later they are bent caudally and ventrally so tha their former ventral surfaces face medially. And finally each limb is rotate about its long axis through an angle of approximately 90 degrees. This rotatio takes place in opposite directions in the arm and leg. The arm is turned outwar so that the thumb comes to lie on the lateral (outer) margin of the limb and th palm faces ventrally (in supination), while the leg rotates inward and the grea toe comes to lie on the medial margin of the limb, and the plantar surface of th foot faces dorsally.

In embryonic life the development of the arm precedes that of the leg and it i not until after birth that the lower extremity exceeds the upper one in lengtl In postnatal life the lower limb increases in length more rapidly than the uppe at about two years their length is equal and in the adult the lower limb is abou one-sixth longer than the upper. The adult relations of the different segments c the limbs (arm, forearm and hand, and thigh, leg and foot) are practically estak lished early in prenatal life although there is some reduction in the relative lengt of the hand and height of the foot in the postnatal period.

THE GROWTH OF THE BODY AND ITS PARTS

Growth of the body in weight.—The diameter of the ripe human ovum i approximately 0.1 mm. Consequently, if the egg-cell is considered as a perfec sphere, its volume is about 0.0000005 cc. and its weight, assuming the specifi gravity to be 1.0, is about 0.0000005 gm. If the average weight of the body in th third decade be considered as 65 kilos (about 143 pounds) we may estimate th total increment in the body-weight during the developmental period at about 13 billion-fold. Considered from this point of view almost all of the weight incre ment takes place in prenatal life, for in this period the body increases in mas about 6.5 billion times while from birth to maturity the gain is but twenty-fold From the standpoint of absolute growth, on the other hand, the body acquire about 5 per cent. of its adult weight before birth and about 95 per cent. thereafter The growth of the body in weight is indicated in the following tables.

Growth in length.—Growth in length has certain characters in common witl growth in weight although the relative lineal increase of the body in the developmental period is obviously much smaller than the relative growth in mass

At the end of the first fetal month the length of the embryo is approximatel 0.25 cm. This is increased 10-fold in the second fetal month but thereafte the relative rate of growth becomes progressively slower. The period of mos rapid absolute growth in length is in the fourth fetal month, during which ther is a gain of about 8 cm. (from 10 cm. in the twelfth week to 18 cm. in the sixteenth). After this there is a gradual decline in the absolute as well as th relative rate of lineal increase.

PRENATAL GROWTH IN LENGTH AND WEIGHT

Age in lunar months	Crown-rump or sitting height (Mall), cm.	Crown-heel or standing height (Mall), cm.	Weight at end of month, grams	Ratio of increase to weight at beginning of month
0	(diameter of ovum = 0.1 mm.)	....	(Ovum = 0.0000005 g.)	....
I	0.25	0.25	0.004	7999.99
II	2.5	3.0	2.0	499.0
III	6.8	9.8	24.0	11.0
IV	12.1	18.0	120.0	4.0
V	16.7	25.0	330.0	1.75
VI	21.0	31.5	600.0	0.82
VII	24.5	37.1	1000.0	0.67
VIII	28.4	42.5	1600.0	0.60
IX	31.6	47.0	2400.0	0.50
*X	33.6	50.0	3200.0	0.33

* 270 days (Mall).

verage Physical Measurements of American Children in the First Four Years of Postnatal Life. (Based in part on the figures of Crum and Taylor.)

Age	Sex	Weight, pounds	Height, inches	Chest girth, inches	Head girth, inches
Birth	Boys	7.3	20.5	13.0	14.0
	Girls	7.1	20.0	12.9	13.8
6 months	Boys	18.0	26.5	17.4	17.4
	Girls	16.7	25.9	17.1	17.1
12 months	Boys	21.9	29.4	18.6	18.5
	Girls	20.7	28.9	18.1	18.0
18 months	Boys	24.6	31.7	19.1	19.1
	Girls	23.4	31.1	18.6	18.5
2 years	Boys	27.1	33.7	19.5	19.4
	Girls	26.4	33.4	19.4	19.0
3 years	Boys	32.2	37.1	20.6	19.9
	Girls	30.5	36.7	20.4	19.4
4 years	Boys	35.9	39.5	21.1	20.1
	Girls	33.7	39.0	20.4	19.7

Growth in Relative Volume of the Parts of the Body.
In per cent. of the total body volume.

	Head and neck	Trunk	Arms	Legs
econd fetal month	45	50	3	3
ixth fetal month	37	40	8	15
irth	27	49	9	15
wo years	22	50.5	9	17.5
ix years	15	51	9	25
laturity	7	53	10	30

The growth in length in fetal life is indicated in a preceding table (p. 20) nd by the upper curve in fig. 21. The age of the fetus may be estimated from s standing height by 'Hasse's rule'; namely: that before the fifth month the ge in fetal months is equal to the square root of the total (standing or crown-eel) height, while after the fifth month the age equals one-fifth of the standing eight in cm. This give approximate results except for the first 2 months.

The length of the body at birth usually falls between 48 and 52 cm. (approxi-nately 19 to 21 inches). The birth-length, like the birth-weight, is influenced y sex, race, and a number of other factors. In the neonatal period there is ften a slight decrease in length due to changes in bodily proportions in the ecovery from the molding effects of birth.

The curve of postfetal growth in length is a sinuous one similar to the curve f postnatal weight increase and the same phases may be recognized in it. Length ncreases about 30 per cent. (15 cm. or 6 inches) in the first six months and about 0 per cent. (25 cm. or 10 inches) in the first year (fig. 22). During early and niddle childhood the lineal increase is very slow, averaging only about 6 or 7 cm. er year. The prepuberal length increase, like the weight increase, begins arlier in girls than in boys and is completed sooner. The body increases approxi-nately 3.3 times in length during the postnatal developmental period. Growth n length usually ceases at about 18 years in females and soon after 20 in males.

FIG. 21.—CHART OF THE AVERAGE GROWTH IN LENGTH AND WEIGHT IN FETAL LIFE. (Base on the data of Mall, A. W. Meyer and Jackson.)

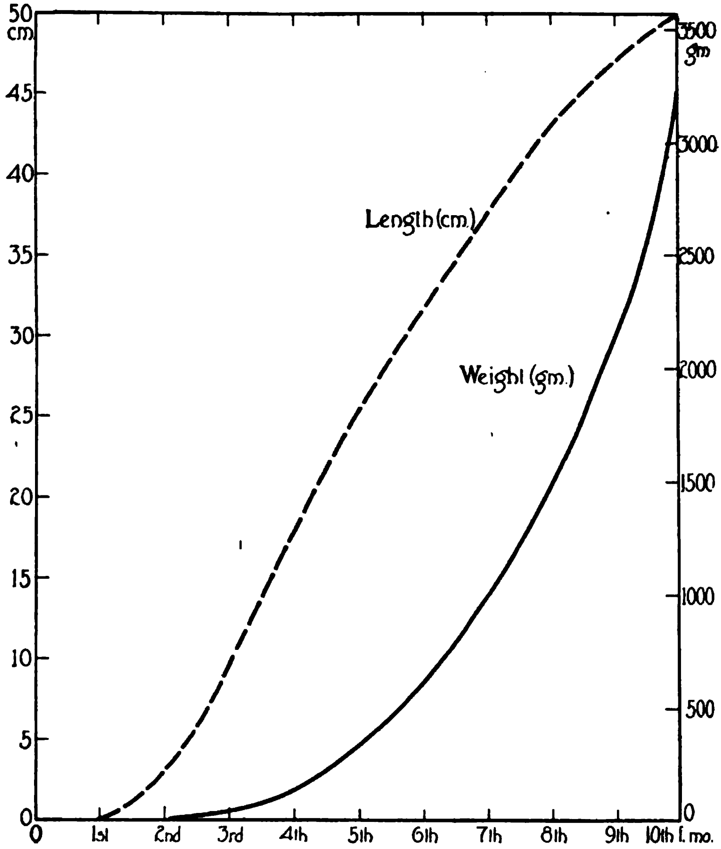
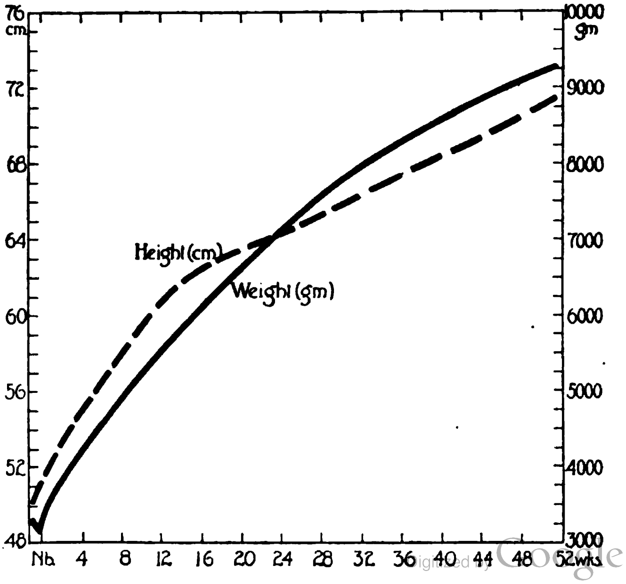


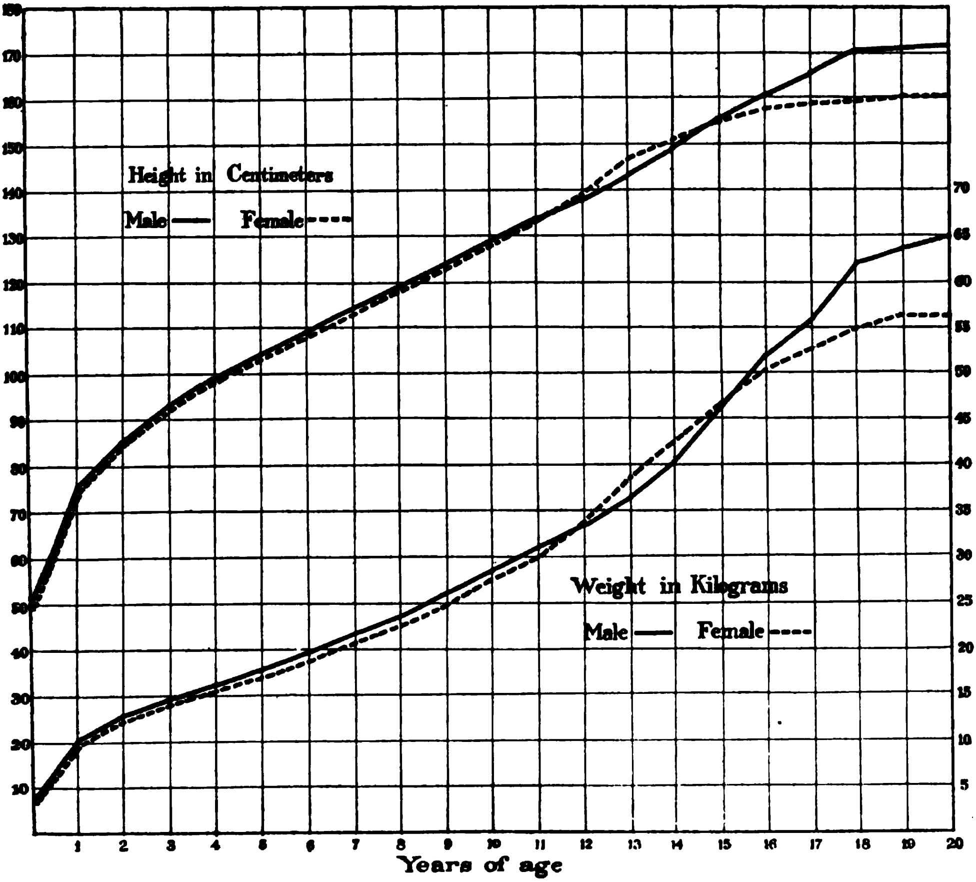
FIG. 22.—CHART OF THE AVERAGE GROWTH IN HEIGHT AND WEIGHT IN THE FIRST YEAR (Bedvel.)



The relation between the length and the weight of the body changes greatly in the developmental period. In later fetal life and early infancy the mass of the body is much greater in proportion to its length than at any subsequent time. The decline in relative weight begins about the middle of the first year and continues until after puberty. Thereafter there is a period of relative mass increase which may continue throughout maturity. During infancy and childhood females are relatively lighter than males but after puberty they are relatively heavier.

The surface area of the body in the developmental period.—The metabolism of the body is greatly influenced by the relation of its surface or cutaneous area to its mass or volume, and this relation is greatly altered in the course of postnatal development. The surface area of the average newborn child is about 2500 square cm. (400 square inches). This is doubled in the first year and is tripled in the middle of childhood. There is a period of rapid increase in surface area before puberty and the total gain between birth and maturity is about 7-fold. But the weight of the body increases approximately 20-fold in this time and there is consequently a great reduction in the ratio of surface area to mass or volume (from over 800 square cm. of surface area per kilogram of body weight in the newborn to less than 300 square cm. per kilogram in the adult.)

FIG. 23.—CHART SHOWING AVERAGE POSTNATAL GROWTH IN HEIGHT AND WEIGHT. (After Stratz.)



The relative growth of the parts of the body.—Growth and differentiation do not take place at the same time or rate in the various parts of the body and the changes in proportions which occur in the developmental period are dependent on this lack of uniformity. While each part passes through its own cycle of changes these changes as a whole tend to follow what is known as the *law of developmental direction;* for it is generally found that development (including growth and differentiation), in the long axis of the body, appears first in the head region of the body and progresses toward the tail region and similarly development in the transverse plane begins in the mid-dorsal region and progresses lateroventrally (in the limbs proximodistally).

Some of the changes in the proportions of the body and the relative size of its several parts are indicated in figs. 15 and 16 and in a preceding table (p. 21). The *head* is the largest part of the body in earlier stages, forming about one- alf of the body in the second fetal month, about one-quarter at birth, and from 6 to 8 per cent. in maturity. The *trunk* as a whole remains of about the same relative size throughout the developmental period (45 to 50 per cent.) although the thoracic portion reaches its maximum in the earlier stages and the pelvic portion not until adolescence. The *lower limbs*, like the pelvis, develop slowly, forming about 3 per cent. of the body at the end of the period of embryo, about 15 per cent. at birth and reaching about 30 per cent. in the adult. The *upper limbs* also form about 3 per cent. of the body weight at the close of the embryonic period. They increase to 8 or 9 per cent. at birth and maintain thereafter about the same relative size.

These changes cause a great increase in the relative weight and volume of the caudal or lower part of the body; and with them the *midpoint* of the body (between crown and sole) is gradually shifted from the upper margin of the thorax at the end of the embryonic period to a level slightly above the umbilicus at birth, and to the level of the crest of the pubis in the adult. The center of gravity is also shifted caudally from the cervical region in the embryo to the point where the inferior vena cava pierces the diaphragm at birth, and to a point just in front of the sacral promontory in the adult.

The relative growth of systems.—There is a marked difference in the growth of the various systems of the body. The *skeleton* grows comparatively slowly during the greater part of prenatal life but increases much more rapidly in the last two fetal months. At birth it forms from 15 to 20 per cent. of the body. Its postnatal growth apparently proceeds with that of the body as a whole, the total increase in weight between birth and maturity being about twenty-fold. The *musculature* also grows rather slowly in the young embryo but increases to about 25 per cent. of the body at birth and to 40 or 45 per cent. in the adult. The blood-vessels apparently also increase in relative weight after birth. The *central nervous system*, on the other hand, is relatively enormous in the young embryo, decreasing from about 25 per cent. of the body in the second fetal month to about 15 per cent. at birth and to between 2 and 2.5 per cent. in the adult. Data for the peripheral nervous system and the skin are somewhat scanty and rather unsatisfactory, but it is evident that both undergo a considerable reduction in relative weight in the postnatal developmental period. The *visceral group* (as a whole) shows a slow but steady decrease in relative weight after the embryonic period, forming about 15 per cent. of the body weight in the second month, about 9 per cent. in the newborn, and from 5 to 7 per cent. in the adult.

Growth of organs.—While in general the individual organs follow the course of growth of the visceral group, each organ has its own characteristic scheme of relative growth. As a rule, after its appearance in embryo, each organ increases more or less rapidly to a maximum relative size, after which, although increasing in absolute size, it decreases in relative size through subsequent prenatal and postnatal life to maturity.

Curves of the absolute growth of the various organs in the period of the fetus all appear much alike, showing an initial period of slow increase followed after the fifth month by a terminal phase of rapid growth. This uniformity is lost at birth and most of the major organs, on the basis of the course of their postnatal growth, can be classified in 4 main groups—splanchnic, nervous, genital and lymphoid (fig. 24).

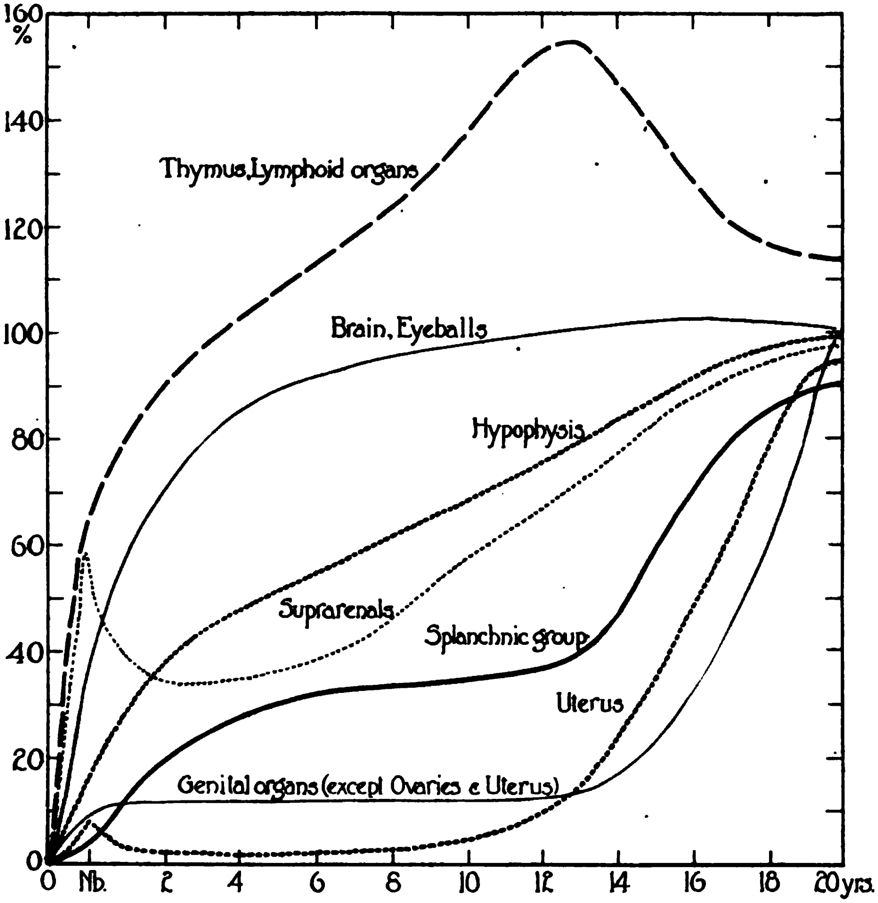
The *splanchnic group* includes the digestive, respiratory, urinary organs, the thyroid gland, the heart, and the spleen. These organs increase rapidly in weight in infancy and the first part of early childhood. In the latter part of early childhood and in middle childhood they grow quite slowly. They enter on a second phase of rapid growth in the prepuberal period, and this is followed by a terminal phase of slow increase in adolescence. In general the growth of the organs of this group is similar to the growth of the body as a whole.

The *nervous group* includes the brain, spinal cord, and eyeballs. These structures grow very rapidly in infancy and have completed over 90 per cent. of their postnatal increase by the close of early childhood.

The organs of the *genital group* (all genital organs with the exception of the ovaries and uterus) grow very slowly until the prepuberal period, when they enter on a phase of rapid increase which extends into or through adolescence.

The structures of the *lymphoid group* (excluding the spleen but including the thymus) are large at birth, grow rapidly until puberty, and then decline in absolute weight.

FIG. 24.—CHART ILLUSTRATING THE COURSE OF GROWTH OF THE VARIOUS TYPES OF ORGANS. The growth of the various organs is calculated in per cent. of their adult weight.



The organs which do not fall under any of the preceding categories are the suprarenal glands, the ovaries, the uterus and the hypophysis. Their growth is considered in connection with their development in the following sections.

THE SKELETON

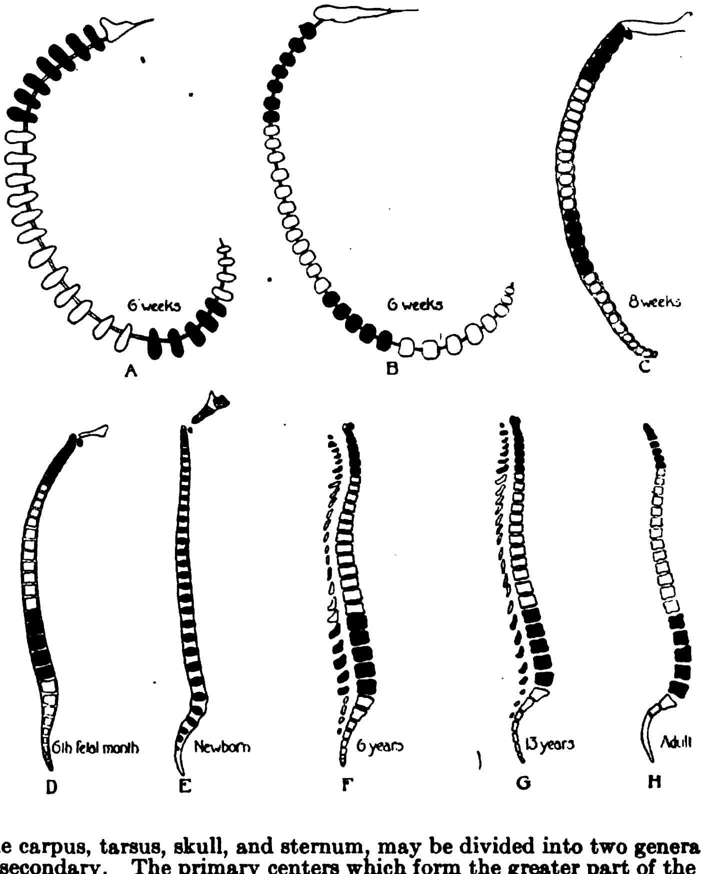
The skeleton, including the bones, cartilages, ligaments, and joints, is derived from the mesoderm. The process is inaugurated by the formation, in the future skeletal regions, of masses of thickened mesenchyma known as scleroblastema. The hard parts of the skeleton, the bones and cartilages, arise in the more condensed parts of the scleroblastema while the joints are formed from the intervening portions. The majority of the thickened scleroblastemal masses are differentiated into cartilage. Certain of these cartilages persist throughout life while a few may be converted at a later time into fibrous tissue. But by far the greater number are replaced by bone during the later development of the skeleton.

Most of the bones of the body arise through the replacement of previously formed bodies of cartilage by bony material, while a smaller number are formed directly in the membranous scleroblastema. The former are known as cartilaginous or replacement bones and the latter are termed membranous or investment bones. All the bones of the extremities, the bones of the spinal column and thorax, the auditory ossicles, the hyoid bone, and the greater part of the bones of the base of the skull are cartilaginous bones. The bones of the face and the greater part of the vault of the skull are membranous bones. Certain of the skull bones are formed partly in membrane and partly in cartilage.

The **process of ossification** begins in discrete foci which are known as centers of ossification. These centers are formed from time to time throughout the developmental period, the first appearing in the clavicle in embryos of the sixth week and the last, in the epiphyses of the vertebral column, in the third decade of postnatal life. Over eight hundred centers are formed in the body and of these slightly more than half appear after birth.

Almost all bones of the adult are formed from one or more centers of ossification; the relation of the total number of bones in the mature skeleton to the total number of centers being approximately as 1 to 3. The ossification centers of all bones of the body with the exception of those of the carpus, tarsus, skull, and sternum, may be divided into two general classes, the primary and secondary. The primary centers which form the greater part of the bone almost always appear before birth. Such centers, when located in long bones, are known as diaphyses. The secondary centers or epiphyses are, with one or two exceptions, formed during postnatal life. A further consideration of the nature of diaphyses and epiphyses will be found in the section on Osteology (p. 82).

FIG. 25.—MEDIAN SAGITTAL SECTIONS OF THE VERTEBRAL COLUMN AT VARIOUS AGES ILLUSTRATING THE DEVELOPMENT OF THE NORMAL SPINAL CURVATURES. Cervical and lumbar vertebræ indicated in black. (Based in part on the figures of Bardeen, Williams and Cunningham.)



As the formation of new centers and the fusion of older ones proceeds at unequal rates during the first two decades, the number of separate bone masses in the body varies from year to year during this period. The **number of bones** in the average newborn child is 270. This number is reduced in the first 2 or 3 years of life through the fusion of primary centers which are present before birth. From this time until puberty, however, the number increases steadily through the formation of epiphyses and the ossification of the carpus and tarsus. In the fourteenth year there are about 350 separate bony masses in the body. After puberty the number again increases rapidly until nearly the middle of the third decade. Often it is not until middle life that the number of bones is reduced to the usual quota of 206, excluding the smaller sesamoids.

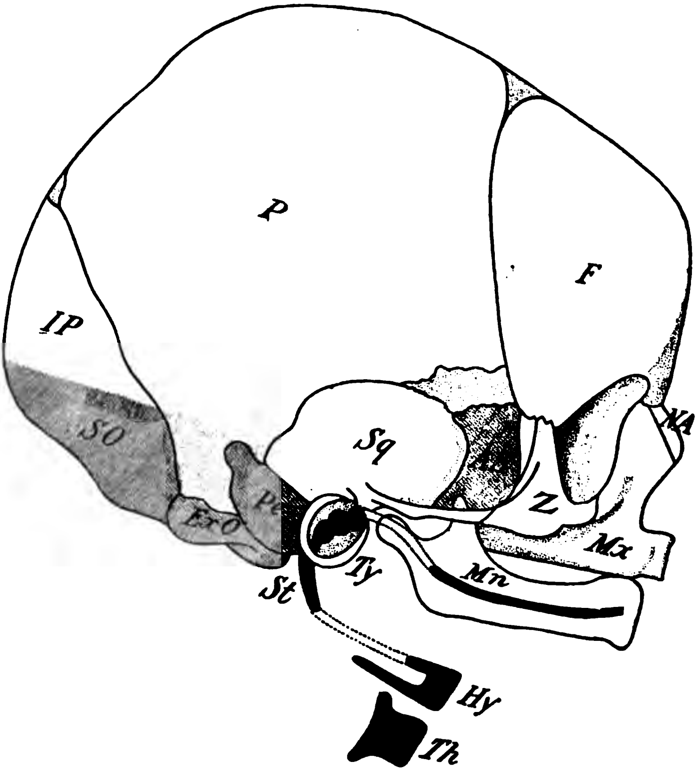
The spinal column.—In the latter part of the first month the notochord is surrounded by a sheath of mesenchyme in which may be recognized segmentally arranged masses which represent the vertebræ and are formed from the sclerotomes of the mesodermic somites. Dorsal prolongations from these masses grow up on either side of the neural tube forming the arches of the vertebræ, and at the same time lateral outgrowths appear which represent the various lateral projections of the vertebræ including the costal processes.

In the second and third fetal months the cervical and sacral regions form the greater part of the vertebral column (fig. 25). At birth the cervical part forms approximately one-fourth, the thoracic part one-half, and the lumbar part one-fourth of the entire movable spine. In the adult the thoracic portion continues to form approximately one-half of the free vertebral column, but the lumbar portion is increased to about one-third, and the cervical portion is reduced to one-fifth or one-sixth of the whole. It is probable that in most cases these proportional postnatal changes take place in the first 3 years.

During the first fetal month the vertebral column shows a pronounced ventral *flexion*. From this time until birth the free portion gradually becomes straighter while the sacral portion first becomes straighter and later acquires a second ventral curve. In the newborn child the free column forms a single gentle curve with an anterior (ventral) concavity extending from the first cervical to the last lumbar vertebra, while the sacrum is directed somewhat posteriorly. The cervical curve appears when the infant begins to lift its head but neither at this time nor later does it become a fixed flexure. The lumbar curve appears as the child assumes the upright posture. It forms very slowly and throughout childhood and adolescence it may be effaced by stretching the spine. Later the lumbar curve is fixed, in a measure, by the anterior thickening of the lower lumbar vertebræ and the intervertebral disks between them. This process begins in later childhood and continues slowly until maturity. For further details on the curvatures, see p. 97.

Fig. 26.—Diagram Showing the Categories to which the Bones of the Skull Belong. (After McMurrich.) The unshaded bones are membrane bones, the heavily shaded represent the chondrocranium, while the black represents the branchial arch elements.

AS, alisphenoid. ExO, exoccipital. F, frontal. Hy., hyoid. IP, interparietal. Z, zygomatic. Mn, mandible. Mx, maxilla. NA, nasal. P, parietal. Pe, periotic. SO, supraoccipital; Sq, squamosal; St, styloid process; Th, thyroid cartilage; Ty, tympanic.



The cartilaginous vertebræ are formed by the appearance of centers of chondrification of the blastemal vertebræ. There are four of these centers for each vertebra, two lateral ones which soon fuse in the body, and one for each side of the vertebral arch. The ossification of the vertebræ is considered in the section on **Osteology.**

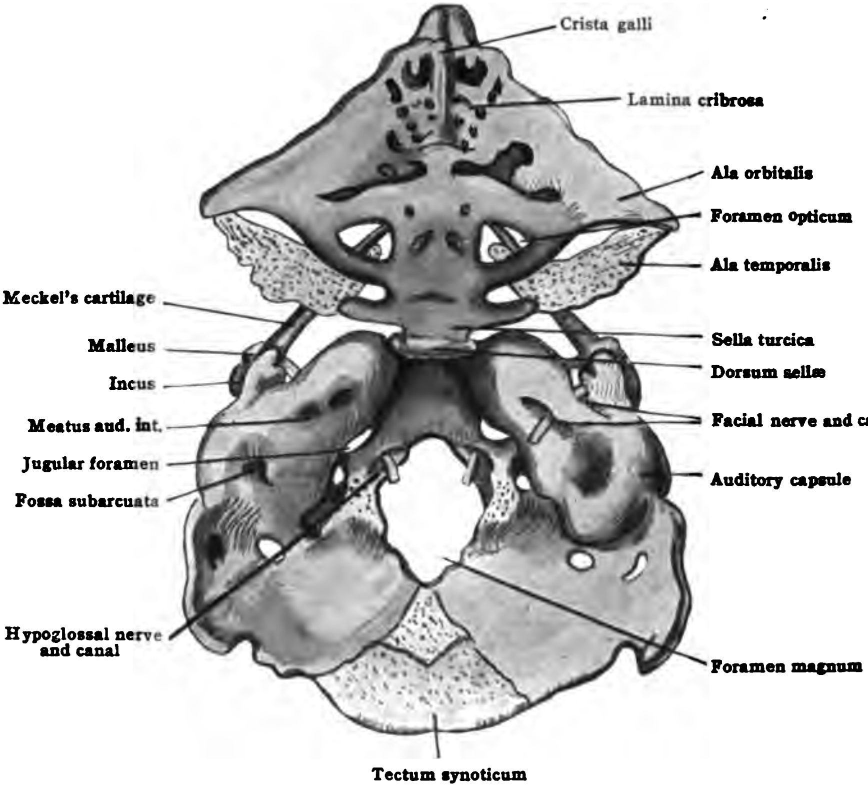
The material between the vertebral masses is later converted into the outer portions of the intervertebral disks; and the segments of the notochord which occupy these regions form the nuclei pulposi. The vertebral portions of the notochord degenerate.

The *length* of the movable or free vertebral column (cervical, thoracic, and lumbar vertebræ) at the end of the second fetal month is about 2 cm. This is more than doubled in the third month, nearly quadrupled in the fourth, and increased almost 10-fold by birth when the average length is almost 20 cm. (8 in.). Between birth and maturity the movable vertebral column increases in length between 2 and 2.5 times, about two-thirds of this growth being accomplished before puberty. After the second fetal month the vertebral column forms from 40 to 45 per cent. of the total length of the skeleton.

Development of the skull.—The bones of the skeleton of the head may be divided into three main categories (fig. 26): (1) the group of cartilage bones developed mainly in the base of the skull around and anterior to the cephalic portion of the notochord and about certain of the organs of sense; (2) the membrane bones which form the vault of the skull and the framework of the upper part of the face; and (3) the cartilage bones which have their origin from the cores of the branchial arches. The distinction between these three parts of the head skeleton is often imperfect, for their parts overlap and fuse during development and the relations between them are constantly shifted and modified.

In the skull, as in the other parts of the skeleton, three stages, the blastemal or membranous, the chondrogenous, and the osseogenous, may be recognized although they overlap considerably and do not proceed at the same rate in all parts of the head skeleton.

FIG. 27.—MODEL OF THE CHONDROCRANIUM OF A HUMAN FETUS 8 CM. IN LENGTH. Cartilage in blue. Viewed from above. (After O. Hertwig.)



Toward the end of the first month the brain is enclosed in a membranous sac formed by the condensation of the surrounding mesenchyma. The basal portion of this sheath forms a thickened plate which surrounds the cephalic portion of the notochord and projects forward beyond its anterior termination. The occipital portion of this plate is greatly expanded and is connected with the fibrous capsules around the developing internal ears. The anterior part of the plate extends forward into the nasal region.

The formation of the *chondrocranium* in the basal portion of the cranial blastema begins early in the second month and is practically complete by the close of the third (fig. 27). The caudal or occipital portion of the chondrocranium forms almost a complete ring around the foramen magnum and extends laterally about the base of the posterior part of the brain. Lying anterior to the occipital portion of the skull on either side are the cartilaginous auditory capsules. The contiguous borders of the occipital portion of the skull and the auditory capsules are partly fused, but lacunæ in this region indicate the position of the future hypoglossal and jugular foramina and transmit the structures which pass through these openings in the adult skull. A median bar of cartilage, which represents the basilar portion of the occipital bone and the body of the sphenoid, passes forward from the anterior margin of the foramen magnum and terminates in an expanded frontonasal plate. Two pairs of processes arise from this median mass. The posterior (alisphenoid) represents a part of the greater wing of the sphenoid and the anterior clinoid processes. The latter fuse with the frontonasal plate enclosing the optic foramina. The medial portion of the frontonasal plate extends forward into the nasal region forming the fundament of the ethmoid bone and a part of the nasal capsule. The lateral portions (orbitosphenoid) spread over the eyes and represent the lesser wings of the sphenoid.

The *visceral elements of the skull* are derived from cartilages formed in the branchial arches. That of the first arch is known as Meckel's cartilage. It extends from the outer surface of the auditory capsule through the mandibular process to the ventral median line. The upper portion of Meckel's cartilage is differentiated into two parts which form two of the auditory ossicles, the malleus and the incus. The lower part is enclosed in a sheath of membrane bone which forms the mandible (fig. 28). All of this part of the cartilage disappears with the exception of its medial tip which is probably involved in the formation of the mental protuberance. The upper portion of the cartilage of the second or hyoid arch forms a portion of the stapes and a part of the styloid process of the temporal bone while its lower segment gives rise to the lesser cornu and a part of the body of the hyoid bone. The upper portions of the third, fourth and fifth arches form no permanent structures. The lower part of the third arch gives rise to the greater cornu and a part of the body of the hyoid bone, and the lower parts of the fourth and fifth arches are involved in the formation of the thyroid cartilage.

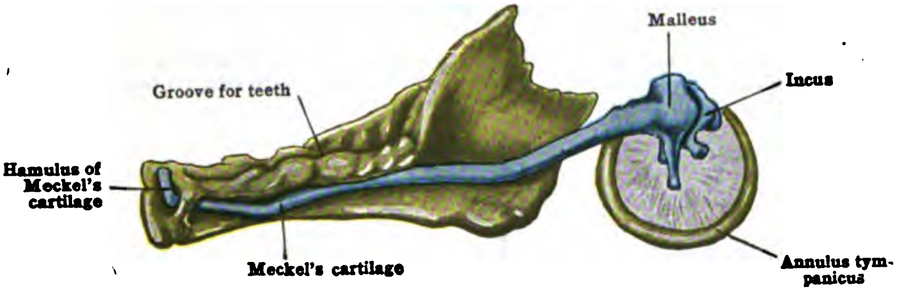


Fig. 28.—Mandible Showing Relations of Meckel's Cartilage in a Human Fetus of 8 Cm. Crown-rump Length. (After Kollmann.)

The further history of the ossification of the bones of the head will be found in the section on **Osteology.**

Growth of the skull.—The most striking characteristic of the fetal skull is the great predominance of the neural over the visceral portion. During the period of the chondrocranium the base of the cranium is large as compared with the roof or vault but with the growth of the cerebral hemispheres the vault becomes increasingly prominent. In early stages of development the occipital region forms by far the largest part of the cranium. Later the parietal portion enters on a period of rapid growth and becomes the predominant region, and finally in the last fetal months the frontal region becomes the center of most vigorous expansion.

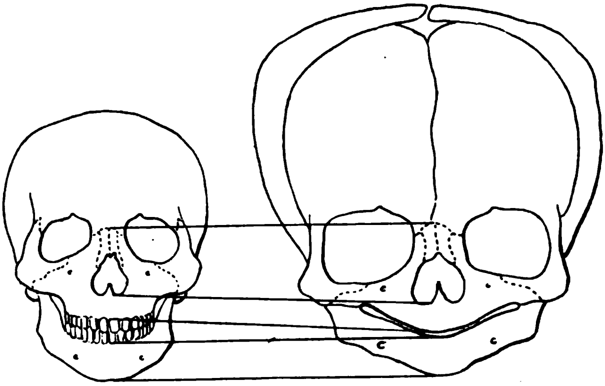


Fig. 29.—Skulls of the Newborn and Adult. Drawn to the same face height to illustrate the relative proportions of the facial and neural skeleton at birth and in maturity. (After Holl.)

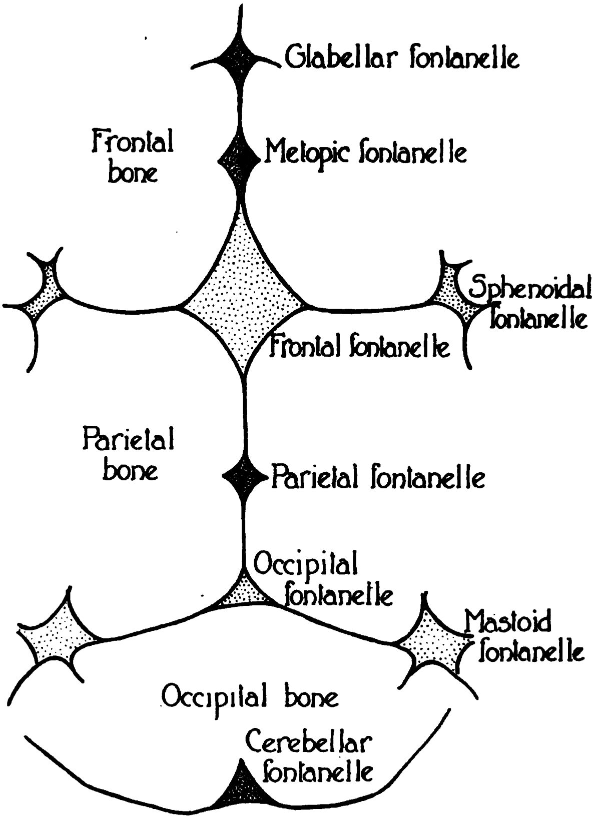
At birth the skull is large as compared with the rest of the skeleton. The neural portion is still much larger than the visceral or facial, the relation between the two being as 8 to 1 as compared with the ratio of 2.5 to 1 in the adult (fig. 29). The vault in comparison with the base of the cranium is also much larger than in later life.

The bones of the cranial vault are quite thin and are separated by narrow strips of membrane which are expanded at the angles of the parietal bones into areas of some size which are known as *fontanelles.* Theoretically fontanelles may be formed at any point on the calvarium which is equidistant from three or more contiguous centers of ossification. There are some 26 such points on the vault of the skull and constant or occasional fontanelles have been found in most of these locations. Two median and single fontanelles (the frontal and occipital), and two lateral and paired fontanelles (the sphenoidal and mastoid), are commonly present at birth. Their positions are shown in figs. 30 and 188–190. Besides these constant fontanelles, numerous accessory ones may be present. The more important ones, the parietal, cerebellar and metopic fontanelles, are all located along the sagittal suture.

The involution of the frontal fontanelle usually begins some months after birth and is generally completed early in the second year. The occipital fontanelle is generally closed by the end of the first trimester. The sphenoidal fontanelle commonly closes in the first 6 months and the mastoid fontanelle between 12 and 18 months after birth. The obliteration of the fontanelles takes place by the progressive ingrowth of the edges of the bone which bounds them, but occasionally separate ossification centers may arise within them and form independent bones which occupy all or part of the original space.

The skull as a whole grows less in postnatal life than the other divisions of the skeleton, the neural portion increasing in volume about 5 times and the facial portion about 12-fold. Between birth and maturity the *cranial capacity* rises from 400 to 1500 c.c. and the horizontal circumference of the skull from about 32 cm. to 48 or 50 cm. Most of this growth takes place in the first two or three years after birth (fig. 31). The postnatal growth of the skull is closely associated with the growth of other structures of the head and particularly with those of the brain and eyeballs, the teeth and paranasal sinuses, and certain of the larger muscles. These structures influence the growth of the skull at different periods: the brain and eyeballs mainl in infancy and early childhood, the teeth and paranasal sinuses mainly in middle and late childhood, and the muscles mainly in adolescence.

Fig. 30.—Diagram of the Calvarium at Birth, Showing the Positions of the Constant and the more Important Accessory Fontanelles. Constant fontanelles shaded in light stipple, accessory fontanelles in heavy stipple.



During infancy all parts of the skull grow rapidly, the cranial capacity increasing from 400 cc. at birth to 700 cc. at 6 months and over 1000 cc. at 18 months. The face grows eve more rapidly than the cranium in this period, the ratio between the two being reduced from to 8 at birth to 1 to 6 in the second year. Most of the early growth of the face is due to th expansion of the orbits, which accomplish over half of their postnatal growth in the first 2 years but there is also a marked growth of the maxillæ and mandible in connection with the development of the deciduous dentition.

From 2 to 7 years the growth of the skull is continued, although less rapidly than in infancy The cranium expands slowly, the vault growing more than the base. The facial skeleton grow more rapidly than the neural portion and by 5 years the ratio between them is 1 to 5. Mos of the growth is in the lower part of the face and is due to the expansion of the dental arche and the development of the maxillary sinuses.

In middle and later childhood the skull grows little, aside from the lengthening of the fac which accompanies the establishment of the permanent dentition. In adolescence the growt of the skull again increases. The cranium enlarges slightly in all diameters, mainly throug the increase in the thickness of the bones of the vault, and the face completes its growth wit the full development of the paranasal sinuses and the upper and lower dental arches. As a rule these later changes are more extensive in the male than in the female skull.

The thorax.—The formation of the thorax is first indicated in the blastemal period by the development of the costal processes of the thoracic vertebræ. These structures represent the future ribs. They assume a rod-like form and rapidly grow ventralward in the thoracic body wall. Their distal ends unite craniocaudally, forming longitudinally directed sternal bands on either side of the ventral midline. The fundament of the unpaired sternum is formed by the side-to-side union of these bands, together with a small mass (the episternum) which is derived from a band of thickened mesenchyma connecting the sternal ends of the developing clavicles.

Fig. 31.—Tracings of Median Sagittal Sections of the Skull at Different Ages, Illustrating the Rate of Growth of the Cranium. (Based on the figures of Corrado and Welcker.)

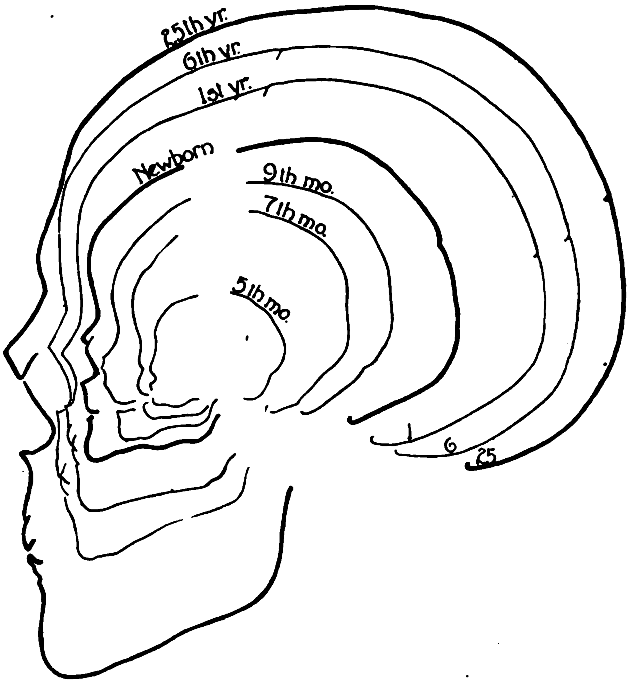
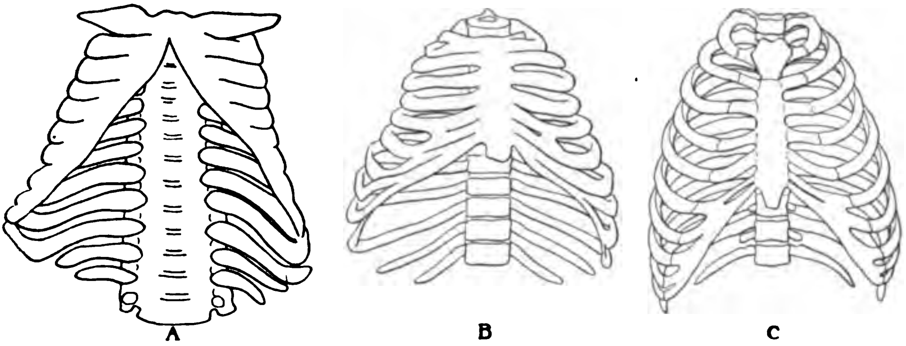


Fig. 32.—Anterior Views of the Skeletal Thorax.
A, of an embryo 15 mm. long. (After Müller.) B, of a newborn child. C, of an adult. All drawn to the same absolute size.



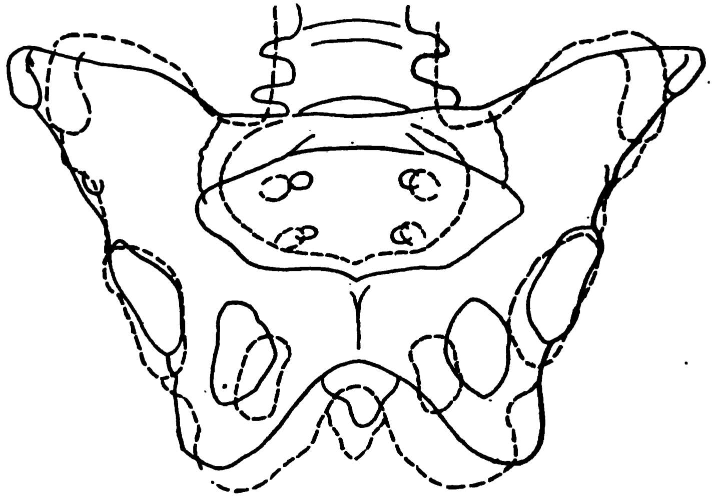
Some of the later changes in the *form of the thorax* are shown in figs. 32, A, B and C. In early stages the thorax is conical and is nearly circular in cross-section. At the time of their origin the ribs lie parallel with one another and are almost horizontal, but they soon incline downward (figs. 44, 45). After birth and particularly after the erect posture is assumed there is a progressive reduction of the relative anteroposterior diameter of the thorax and its base is relatively contracted. These changes are possibly due in part to the effect of gravity on the viscera and to the reduction in relative size of the organs of the upper abdominal region.

The postnatal growth of the thorax, as determined by external measurements, particularly of the horizontal chest circumference, seems to follow the course of the growth of the body in height and weight. There is a period of rapid increase in infancy and a part of early childhood, a period of slow growth in middle childhood, followed by a phase of rapid growth in prepuberty and perhaps early adolescence, and finally a terminal period of slow increase to maturity.

The pelvis.—The pelvis is formed in part from the fixed vertebræ of the sacrum and coccyx, which are developed around the lower portion of the notochord, and in part from the blastemal ossa coxæ which are developed from the proximal portions of the mesenchymal cores of the lower limb-buds. These elements are not closely associated at the time of their differentiation and the complete pelvic girdle with definite fundaments of the pubic symphysis and the sacroiliac articulations is not established until about the end of the second month. In early fetal life the pelvis is relatively small. After the third month all of the pelvic diameters grow at approximately the same rate and there are no great changes in the shape of the pelvis from this time to birth.

The *pelvis of the newborn* differs from that of the adult in a number of particulars (fig. 33). It has a distinctly conical form and its length is greater in proportion to the transverse and conjugate diameters. The pelvic cavity is relatively as well as absolutely much smaller than in the adult. The superior aperture approaches a circle more closely than in later life, although even at birth the transverse diameter is greater than the conjugate. The dimensions of both the lesser pelvic cavity and the inferior aperture are smaller in proportion to the superior aperture than at maturity. The sacrum forms a greater portion of the pelvic circumference and is less depressed between the ilia. The sacral promontory is less marked, but a second prominence may be indicated at the level of the linea terminalis. There is little indication of the sacral concavity. The acetabula are very large and shallow at birth while the obturator foramina are relatively small. The pelvis is more vertical in position than later, the plane of the superior aperture forming an angle of 80° in the horizontal as compared with 50° to 60° with the adult, while the long axis of the symphysis pubis is more nearly perpendicular.

FIG. 33.—DRAWING OF ANTERIOR VIEWS OF THE PELVES OF AN ADULT MALE AND A MALE NEWBORN DRAWN TO THE SAME ABSOLUTE SIZE AND SUPERIMPOSED. Adult pelvis in solid line, newborn pelvis in broken line. (After Merkel.)



During the first 2 years of life the pelvis grows rapidly in all dimensions. This growth is continued at a slower rate from 2 to 5 years, but there is comparatively little increase between 5 and 10 years. There is a second period of more rapid growth in later childhood and adolescence, and by the end of the second decade the pelvis has almost obtained its adult dimensions, although many of the pelvic epiphyses do not unite with the main bones until the twenty-fifth year.

Until the infant assumes an erect position, the pelvis changes but little in form. As this position becomes habitual, the sacrum descends between the ilia and the promontory is definitely established. With this there is a relative expansion of the ala of the ilia, an increase in the pubic angle and a bending of the sacrum backward. The increase in the transverse diameter of the pelvis is brought about mainly by the growth of the sacrum and the posterior parts of the ilium. Growth also takes place along the line of apposition of the three divisions of the os coxæ in the acetabulum, but there is probably comparatively little growth, at least in males, at the symphysis pubis. The pelvic growth which occurs after puberty is practically all epiphyseal.

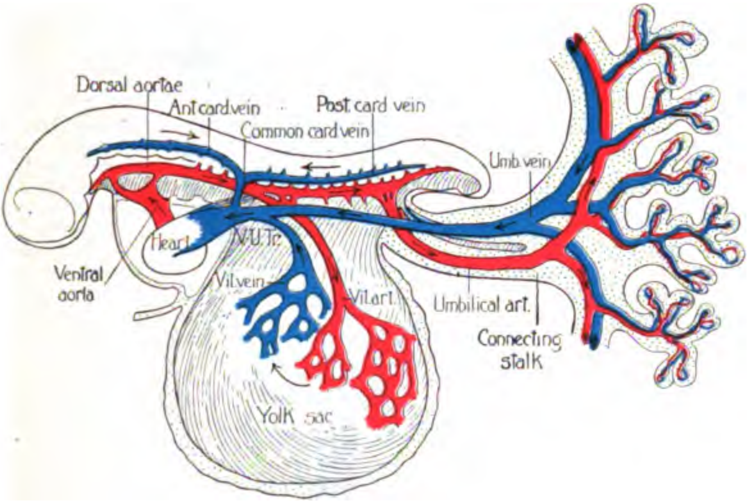
Sexual differences in the pelvis appear about the sixth fetal month, mainly in the form of differences in the pubic angle and the shape of the ilia. The pelvis of the newborn male is larger than that of the female, the sacrum is relatively wider, the ilia less vertical, the pubic angle more acute and the acetabula shallower and more horizontal. The sexual differences of the newborn pelvis, aside from those of size, are usually masked in the early period of rapid growth and do not reappear until the prepuberal period. During the first decade the pelvic measurements of boys are usually larger than those of girls, but after this time the dimensions of the female pelvis are generally the greater.

THE VASCULAR SYSTEM

In this section the consideration of the vascular system will be limited to a description of the establishment and course of the early embryonic circulation, an account of the fully established circulation of the late fetus, and the changes in the circulatory system at birth; including an outline of the general growth of the vascular structures. The morphologic changes by which the various segments of the embryonic circulatory system are transformed to the adult structures are described in connection with the Vascular System (pp. 668 and 724).

In man and the higher mammals the development of the vascular system is extremely precocious, due to the small amount of food substances stored in the ova of these forms and the consequent necessity of a system of vessels which can draw nourishment and oxygen from the maternal circulation and distribute them to the tissues of the embryo.

Fig. 34.—Diagram of the Circulation of a Young Human Embryo. (Based in part on the figures of Watt and Brödel.)



Fundaments of the first vessels in man appear in the form of cords, cellular strands, and cysts in the extraembryonic mesoderm at a stage preceding the establishment of the embryo on the germinal disk. These structures are organized into two sets of anastomosing cords; one, the umbilical or allantoic, which is associated with the connecting stalk, allantois, and the trophoblast; and the other, the vitelline, which spreads out in the mesoderm of the yolk-sac. Trunks formed from these networks pass, in the mesoderm, to the margin of the germinal disk. As the tubular embryo is formed from this structure, they enter the developing body either as definite trunks or as capillary plexuses, and form the framework of the embryonic vascular system.

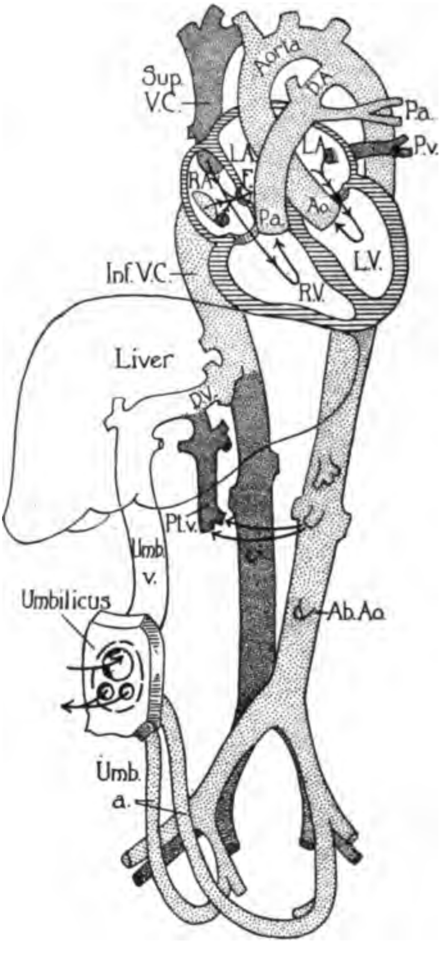
The course of the embryonic circulation.—The form of the circulatory system in the young embryo is illustrated by fig. 34. The blood from the capillaries of the chorion (the modified trophoblast) passes to the embryo through the paired umbilical or allantoic veins. Before entering the embryo these vessels are joined by the vitelline veins which collect the blood from the yolk-sac. These vessels form the vitelline-umbilical trunks (V.U.Tr.) which enter the body, on either side, in the splanchnic mesoderm below the foregut and join in the tubular heart, which is formed from them. From the heart the ventral aortæ pass below and then around the anterior part of the foregut and gaining its dorsal surface run backward as the paired dorsal aortæ. The dorsal aortæ give off the vitelline arteries (Vit. art.) which return blood to he capillaries of the yolk-sac and finally terminate in the umbilical or allantoic arteries which run to the chorion through the connecting stalk and end in the chorionic capillaries. The dorsal aortæ also give rise to a number of segmentally placed arterial sprigs which supply the tissues of the embryo. The blood from these vessels is collected by venules which empty into ongitudinal venous trunks, the anterior and posterior cardinal veins. The cardinal veins on either side drain into a short common cardinal vein (duct of Cuvier) which opens into the posterior part of the heart-tube in common with the vitelline-umbilical trunks.

The umbilical veins are the nourishing vessels of the embryo, since they carry blood from he chorionic capillaries where it has received oxygen and food-stuffs (by osmosis) from the maternal circulation. These substances are absent from the vitelline veins, since the yolk-sac f the human embryo contains no reserve food material. Theoretically, at least, there is a mixture of arterial blood from the umbilical vessels and venous blood from the common cardinal veins in the posterior end of the heart; but the actual difference between the arterial and venous blood in the young embryo is probably very slight since the volume of the blood-stream is elatively large and the rate of circulation presumably very rapid.

The fetal circulation.—The course of the blood in the late fetus is shown in diagrammati fashion in figs. 35 and 586. The pure or arterial blood from the placental capillaries enter the body by the single umbilical vein, and passes through this vessel to the liver where it i joined by a branch of the portal vein carrying venous blood. The blood from the sinus forme by the union of these two vessels passes through the *ductus venosus* which joins with the inferio vena cava (either directly or through the left hepatic vein). As the vena cava is carryin blood from the capillaries of the lower part of the body there is a further mixture of venous an arterial blood at this point. The stream of mixed blood now passes through the terminal portion of the vena cava and enters the caudal portion of the right atrium. The superior vena cava also enters the right atrium, bringing back venous blood from the head and superior extremities. The opening of the superior vena cava with its valves is so placed that the strean from this vessel is directed toward the *foramen ovale* between the right and left atria.

FIG. 35.—DIAGRAM OF THE FETAL CIRCULATION.

Ab.Ao., abdominal aorta. Ao., ascending aorta. D.A., ductus arteriosus. D.V., ductu venosus. F., foramen ovale. Inf. V.C., inferior vena cava. L.A., left atrium. L.V., left ventricle. P.a., pulmonary arteries. Pt.v., portal vein. P.v., pulmonary veins. R.A., righ atrium. Sup.V.C., superior vena cava: Umb.a., umbilical arteries. Umb.v., umbilical vein



Despite this anatomical arrangement, however, experimental evidence indicates that th blood of the inferior and superior venæ cavæ is completely mixed in the right atrium. The blood from the right atrium flows in part into the left atrium, where it is joined by a small stream of venous blood, returning from the lungs through the pulmonary vein. It then passes into the left ventricle and thence to the systemic circulation through the arch of the aorta. A portion of the blood from the right atrium passes into the right ventricle and through it to the pulmonary artery. A small part of this stream is diverted to the right and left pulmonary arteries to supply the lungs, but the main current passes through the *ductus arteriosus* (Botalli to pass into the descending arch of the aorta, joining the stream from the left ventricle which has come through the aortic arch. The blood passing through the aorta continues downward through this vessel, and such as remains after supplying the aortic branches flows into the umbilical arteries and thence back to the capillaries of the placenta.

Several *peculiarities of the fetal circulation* which are particularly striking may be enumerated. But one vessel in the body of the fetus, the umbilical vein, carries strictly arterial blood, and this vessel supplies no part of the body directly, except a small portion of the liver. The blood entering the right atrium from the inferior vena cava has already received venous mixtures from three sources (the portal vein, the inferior vena cava, and the vena azygos major). There is a complete mixture of blood from the superior and the inferior vena cava in the right atrium and a further addition of venous blood from the pulmonary vein in the left atrium. Thus the circulating blood of the fetal body is throughout mixed, venous and arterial. Its efficiency under these conditions probably depends: (1) on its very large quantity compared with the volume of the fetus; (2) on the rapidity of its circulation; and (3), on the relatively slow rate of catabolism (and hence slight amount of waste products) in the fetal organism.

The establishment of the adult circulation.—The change from the fetal to adult type of circulation is brought about by the closure of the fetal blood-passages, the umbilical vessels, the ductus venosus, the ductus arteriosus, and the foramen ovale. In this closure two processes can be recognized; the physiologic occlusion, which takes place immediately after birth, and the anatomical obliteration which occur days, months, or even years later. With the establishment of respiration the ductus arteriosus collapses, and all the blood from the pulmonary artery is forced through the branches of these vessels into the capillary bed of the lungs. This leads to an increased flow from the pulmonary veins into the left atrium and pressure in this chamber rises so that the valve of the foramen ovale is forced against the margin of the interatrial septum and the communication between the two chambers is interrupted. At the same time, with the tying of the umbilical cord, or in most cases even with the simple interruption of this structure, the fetal ends of the umbilical arteries and veins are contracted and their lumina obliterated. With this change, blood no longer flows through the umbilical vein and the current of blood through the ductus venosus ceases.

The actual obliteration of the fetal blood-passages rarely begins in the first fortnight of postnatal life. The obliteration of the ductus venosus is brought about through the interruption of its epithelial lining and invasion of its lumen by the connective tissue of the tunica media and tunica interna. The vessel is generally completely closed by the end of the first month. Obliteration of the ductus arteriosus takes place in much the same way, generally in the first half year of postnatal life, but sometimes not before the close of the first year. The occlusion of the foramen ovale is apparently brought about by the proliferation of connective tissues in the valve and at the margin of the foramen, through the mechanical irritation of these structures by friction in the movements of the heart. At the close of one year the foramen is obliterated in about one-half of all cases, but the opening remains patent to the probe in nearly one-third of adult hearts. The obliteration of the umbilical arteries and vein begin shortly after birth with the organization of the thrombus at the cut end of the vessel; but the process is not complete throughout the intra-abdominal portion of these vessels until several weeks after birth. For changes in the umbilicus, see p. 1403.

The growth of blood-vessels.—In the young embryo the blood-vessels have very thin walls and their caliber is relatively enormous; that of the dorsal aorta, for example, is nearly one-fifth the transverse diameter of the body in the third week. In fetal and postnatal life the blood-vessels continue to increase in absolute diameter even to very old age, but their relative diameter is steadily reduced, at least until maturity. In the developmental period, the different vascular trunks constantly adjust to the changing volumes of the areas which they supply and to modifications in the caliber of vessels which drain from them. Thus the arterial trunks to the head increase in size during the period of rapid growth of this part while those of the lower imbs grow slowly in early life but increase rapidly when these members enter a period of active growth. And the abdominal aorta undergoes an actual decrease in diameter for a period after birth when the umbilical arteries which drain it are obliterated.

The walls of arteries in the fetal period are relatively thicker, compared with the diameters of their lumina, than in postnatal life; but their absolute thickness increases slowly to an advanced age. In fetal life the growth of the walls of arteries takes place almost entirely in the unica media and tunica externa, the tunica interna remaining almost unchanged from the ourth fetal month until birth. After birth, however, the relative growth of the interna is much more rapid than that of the other coats. Apparently there is little growth of the tunica media after puberty although the interna increases throughout postnatal life.

There are but few observations on the growth of vessels in length, but these seem to indicate hat the lineal growth of blood-vessels is closely correlated with the lineal growth of adjacent tructures.

Growth of the heart.—In the second fetal month the heart forms about 3.6 per cent. of the ody. The relative weight decreases to about 0.7 per cent. at the close of fetal life. With the reat increase in the weight of the body in the first year the relative heart-weight drops to bout 0.5 per cent., and from this time there is very slow decrease until the middle years of dult life when the average relative weight of the heart is 0.4 to 0.45 per cent. It should be emembered that during fetal life the heart not only sends the blood through the capillaries f the body but also through those of the fetal portion of the placenta. The relation of the eight of the heart to the combined weight of the body and placenta in the latter fetal months not far from the adult ratio of heart-weight to body-weight (0.47 to 0.45 per cent.).

The growth in absolute weight of the heart in postnatal life follows the course of the visceral roup of organs. The birth-weight of the organ (20 to 25 grams) is doubled in the first year, ipled in 4 years and increased 6 to 8-fold by puberty. The total postnatal gain in absolute eart-weight is usually about 12-fold.

The mass of the walls of the various chambers of the heart is distinctly modified in the deelopmental period. The atria form a considerably larger proportion of the heart-weight in e fetus than in the adult, the reduction in their relative weight taking place mainly in early fancy. In the fetal period the weight of the right ventricle is equal to or greater than that the left. But the additional work which falls to the left ventricle after the separation of the

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systemic and pulmonary circulations at birth causes this portion of the heart to grow so rapidl that by the close of the first year it is nearly twice the weight of the right ventricle.

The lymphoid and sanguifactive organs.—The first *blood-cells* of the human embryo a differentiated in connection with the developing blood-vessels of the yolk-sac; but the liv soon becomes a seat of blood-formation and remains a sanguifactive organ until birth. Tl *bone-marrow* appears as the primary marrow cavities are formed in the course of the ossificatio of the different bones, and since the first ossification centers do not appear until the sixth we there is little differentiation of bone-marrow until after the period of the embryo. The *sple* appears in the fifth week as a thickening of the layers of splanchnic mesothelium of the dors mesogastrium, the splenic pulp being differentiated from a mass of dense mesenchyma forme by the proliferation of cells from the splanchnic layer of the region. The fundaments of lymp glands appear in the third month as collections of lymphoid cells about plexuses of lymphat capillaries. The formation of lymph-glands continues through fetal life and probably for a indefinite time after birth. For development of the lymphatics in general, see LYMPHAT SYSTEM, p. 739.

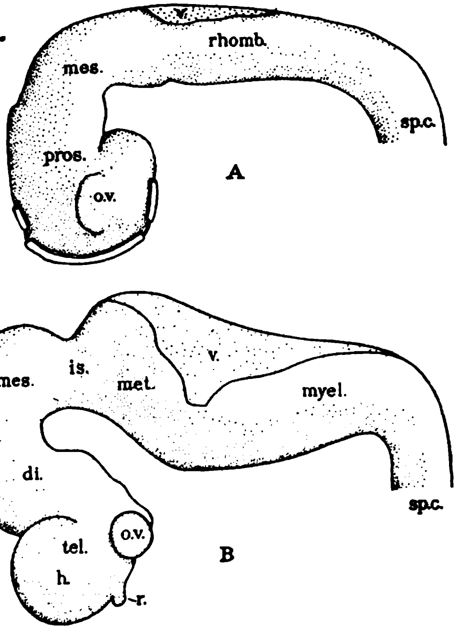
The growth of lymphoid tissue has been considered in connection with the growth of organ It is characterized by a relatively great amount of lymphoid tissue at birth, an increase i absolute amount until about puberty and a subsequent decline in amount both absolute an relative (fig. 24). The spleen, however, does not follow this course. It is relatively small i early fetal life but increases in the latter part of the period, forming about 0.3 per cent. of th body at birth. During postnatal life it declines in relative weight, forming less than 0.2 p cent. of the body in the adult. The increase in the absolute weight of the spleen in postnat life follows the course of the splanchnic group of organs.

THE NERVOUS SYSTEM

The early development of the brain.—Even before the neural plate is folded into the neur tube it is differentiated into an anterior expanded portion which represents the brain and narrower posterior part which represents the spinal cord. As the anterior part of the pla becomes tubular it is further divided by grooves into three swellings or vesicles, the forebrai midbrain, and hindbrain (figs. 36A and B). As these chambers differentiate, the axis of th cephalic portion of the tube is bent first at the level of the midbrain (the cephalic flexure) an soon after at the juncture of the hindbrain at the cord (the cervical flexure). The floor of th middle portion of the hindbrain is curved ventrally at a much later time, forming the third o pontine flexure. For further details and figures of the early development of the brain, see pp 11, 790.

FIG. 36.—A, THE BRAIN OF A 4.0 MM. HUMAN EMBRYO. (From Lewis, after Bremer.) THE BRAIN OF A 10.2 MM. EMBRYO. (From Lewis, after His.)

Except the isthmus, is., the principal subdivisions of the brain are indicated by prefixes the term encephalon. sp.c., spinal cord. h., hemisphere. o.v., optic vesicle. r., rhine cephalon. v., roof of the fourth ventricle.



Before the forebrain is completely closed it is expanded transversely forming lateral out pouchings, the optic vesicles. Each optic vesicle forms a distal optic cup which produces th retina of the eye, while its proximal optic stalk remains attached to the forebrain as the opt

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nerve. The point of attachment of the optic stalks marks the line of division of the forebrain into two secondary vesicles, an anterior telencephalon and a posterior diencephalon. Somewhat later a second pair of lateral outpouchings are formed from the walls of the telencephalon dorsal to the optic evaginations. These are the cerebral vesicles. They form the cerebral hemispheres and (secondarily) the olfactory lobes and tracts. The diencephalon forms a smaller part of the forebrain. Its floor is depressed posterior to the optic stalks, forming the embryonic infundibulum from which are differentiated the posterior lobe of the hypophysis, the mammillary bodies, the tuber cinereum, and the infundibulum of the adult. The lateral walls of the diencephalon are thickened forming the thalamus and geniculate bodies. The roof becomes membranous anteriorly to form the epithelial layer of the tela chorioidea; posteriorly it forms the pineal body.

The walls of the mesencephalon become greatly thickened, their dorsal portion forming the corpora quadrigemina and their ventral portions the greater part of the cerebral peduncles (crura cerebri).

Three secondary divisions can be recognized in the hindbrain or rhombencephalon: (1) a narrow isthmus, which is continuous with the mesencephalon anteriorly; (2) a short middle segment, the metacephalon; and (3) a large posterior portion, the myelencephalon. The isthmus changes little in form in later development. It is represented in the adult by a portion of the brain-stem which includes the anterior medullary velum, and parts of the brachium conjunctivum (superior cerebellar peduncles) and of the cerebral peduncles. The metencephalon forms an expanded and thickened ring of the brain-tube immediately behind the isthmus. Its dorsal part forms the cerebellum and its ventral portion the pons. In early stages the myelencephalon forms a widely expanded chamber with a membranous roof and a thick floor which is continuous with the cord without any sharp line of demarcation. The myelencephalon becomes the medulla oblongata, a part of the roof forming the posterior medullary velum.

The spinal cord.—In the young embryo the spinal cord extends to the extreme caudal end of the body; but with the regression of the tail in the latter part of the second fetal month there may be recognized an anterior or trunk portion which will form the definitive spinal cord, and a posterior or caudal segment which undergoes partial involution, forming the filum terminale. The distinction between these two portions is definitely established before the middle of the third month. The cervical and lumbar enlargements of the cord can be recognized by the end of the third month. For relations at various stages, see figs. 43–48.

The cerebrospinal cavities.—The central lumen of the neural canal is never lost but exists throughout life in a modified form as the central canal of the spinal cord and the ventricles of the brain. The lumen in the lower end of the trunk portion of the spinal cord remains as a chamber of some size, the *ventriculus terminalis*, but in the remainder of the cord it is reduced in relative size through the fusion of the dorsal part of the lateral walls to the minute central canal. In the myelencephalon and the metencephalon the lumen is expanded, forming the fourth ventricle; while in the isthmus and mesencephalon it is reduced to a narrow channel, the Sylvian aqueduct. The third ventricle represents the expanded anterior end of the canal in the forebrain and the lateral ventricles its lateral extensions which are produced with the evagination of the cerebral vesicles, the points of origin of these extensions being represented by the interventricular foramina. The epithelial layers of the choroid plexuses which project into the third and fourth ventricles are formed by the invaginations of the membranous wall of the brain in these regions and the morphologic continuity of the walls of the canal is not interrupted, at least during the embryonic and the early fetal periods. The so-called fifth ventricle (cavum septi pellucidi) has no developmental relation to the cerebrospinal cavities, being formed much later between the apposed medial walls of the hemispheres.

Growth of the central nervous system.—The relative weight of the central nervous system in the developmental period has been considered in connection with the general growth of systems. The absolute weight of the *brain* at the end of the third fetal month is about 3.5 gm. This is increased about 10-fold by the middle of the fetal period and about 100-fold by birth. The weight of the *brain* is more than doubled in infancy and is increased about 3-fold by the close of the first period of childhood. Thereafter the rate of absolute growth is very slow, the adult weight, which is about 3.6 times that of the newborn, being commonly attained by the close of the fifteenth year.

The *spinal cord* weighs about 0.15 gm. at the close of the third fetal month, increasing about 5-fold by the middle of the fetal period and 20-fold by birth. The cord increases about 8-fold in postnatal life, most of this growth taking place in infancy and early childhood. The spinal cord forms about 15 per cent. of the central nervous system in the second fetal month but thereafter it forms a decreasing proportion until birth when it is less than 1 per cent. In postnatal life, on the other hand, this ratio gradually rises to about 2 per cent.

The parts of the brain also show changing relations in relative size during the developmental period. The *brain-stem* follows the course of the cord, forming a larger proportion of the brain in fetal life, a gradually decreasing proportion in the later part of prenatal life, and a small relative increase after birth. The *cerebellum*, on the other hand, grows very slowly in early fetal life but in the later fetal months enters a period of rapid relative growth which continues through infancy and early childhood. It forms about 3 per cent. of the brain in the third fetal month, about 6 per cent at birth, and about 10 per cent. in maturity. For topography of the developing brain, see figs. 43–48, also fig. 746.

The development of the peripheral nerves.—When the neural tube separates from the surface ectoderm there is left between these two structures a narrow plate of ectodermal cells known as the neural crest. These cells give rise to all of the sensory nerves of the cerebrospinal system, with the exception of the optic and olfactory nerves whose development is considered in connection with the sense organs. The motor nerves and the motor portions of the mixed nerves, on the other hand, are all formed as processes from cells located in the ventral or ventrolateral portion of the neural tube. The course of development of the spinal and cranial nerves is described in the section on the NERVOUS SYSTEM.

The eye.—Four elements enter into the formation of the main structures of the eye. These are: (1) the optic vesicle, derived from the lateral wall of the forebrain; (2) the lentic or optic placode, formed by a thickening of the surface ectoderm over the optic vesicle; (3) a zone of surface ectoderm immediately surrounding the lentic placode but which does not share in its thickening; and (4) the head mesenchyma which surrounds the optic vesicle and placode.

The optic vesicle gives rise to the retina (both nervous and pigmented layers), the epithelium covering the posterior surface of the iris and ciliary body and the optic nerve. The lentic placode is converted into a lentic vesicle which later forms the lens. The surface ectoderm immediately surrounding the lentic placode produces the anterior epithelial layer of the cornea, the epithelium of the conjunctiva and the parenchyma of the lacrimal gland. The surrounding mesenchyma forms the sclerotic and choroid coats of the eye and their derivatives. The vitreous body is probably derived in part from the ectodermal and in part from the mesenchymal elements of the eye. The further history of the eye is described in connection with the section on the SPECIAL SENSE ORGANS (p. 1114).

The ear.—As has been previously described (pp. 17, 29), the outer ear is formed from the first branchial groove or cleft, the middle ear is a derivative of the first branchial pouch, and the auditory ossicles are formed from the upper ends of the cartilages of the first and second branchial arches. The inner ear is formed from the otocyst, a closed sac formed from the otic or auditory placode which appears as a thickening of surface ectoderm above the first branchial arch. The development of the ear is considered in more detail in the section on the SPECIAL SENSE ORGANS (p. 1129).

The ear in childhood.—The ear of the newborn and infant differs from that of the adult in several important details. The external auditory meatus is relatively short and straight and there is no true bony meatus. The tympanic membrane is slightly smaller than in the adult, but it acquires its full size in infancy. It is slightly more horizontal in early life. The tympanic cavity and ossicles have reached their full size at birth and the epitympanic recess and antrum are quite as large as in maturity if not larger. The antrum lies entirely above the tympanic cavity and its lateral wall is only about 1 mm. thick. The mastoid process does not develop until after the first year and the mastoid cells usually appear in later childhood. The auditory (Eustachian) tube has about one-half of its adult length at birth but its diameter is quite as great as in maturity. The tube is almost horizontal in the infant, the oblique course of the adult tube being acquired with the growth of the nasopharynx in middle and later childhood. The internal ear has practically its adult dimensions at birth.

The olfactory organ.—The organ of smell is developed from the epithelium of the upper part of the nasal fossæ, whose history is described later in connection with the development of the digestive tract. The olfactory nerve is formed by the processes of specialized cells which remain in the olfactory mucosa. A rudimentary olfactory organ, the *organ of Jacobson*, is represented in the embryo by a pair of small pouches in the nasal septum. These usually disappear in the later part of fetal life.

THE DEVELOPMENT OF THE DIGESTIVE TRACT

Early development.—In the early embryo four main structures may be recognized which play a part in the later development of the digestive and respiratory tracts. These are: (1) the nasal pits and (2) the oral sinus, which are lined with ectoderm derived from the covering of the inferior surface of the head; (3) the archenteron, formed from the entoderm of the roof of the yolk-sac; and (4) the cloacal membrane. These elements form the epithelial linings of the digestive and respiratory tracts and the parenchyma of the glands connected with them. At a later time there is associated with them a considerable amount of mesenchyma which gives rise to the muscular wall and the connective tissue investments of the tubes and to the supporting framework of the associated glands.

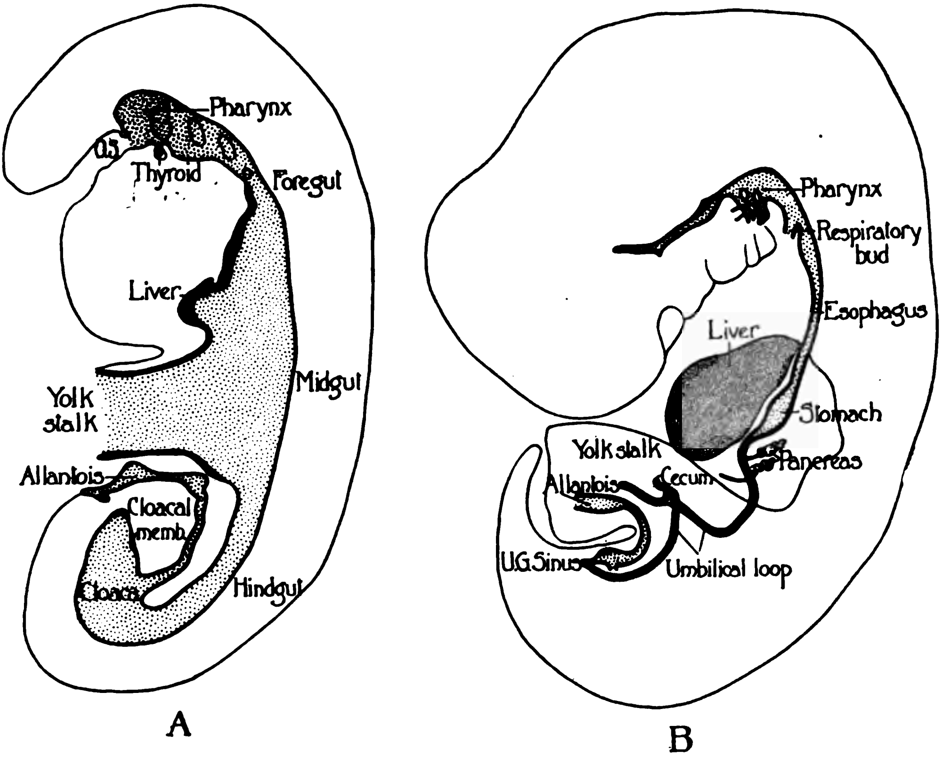
Some of the general changes in the development of the digestive tract are shown in figs. 37, 43, 44, 45 and 46. The oral sinus is deepened and its roof gives rise to a median pocket (Rathke's pouch), which later separates and forms the anterior lobe of the hypophysis. At the same time the *buccopharyngeal membrane* separating the sinus from the cephalic end of the pharynx disappears and the ectoderm and entoderm becomes continuous in this region. The foregut is differentiated into an upper expanded pharynx and a lower tubular segment which later forms the esophagus, stomach, and a portion of the duodenum. The *midgut* elongates and its connection with the yolk-sac is reduced to a slender yolk-stalk. The *hindgut* is differentiated into an upper tubular portion and a lower chamber, the *cloaca*. The latter gives origin to the allantois and its floor is formed in part by the cloacal membrane. The cloaca is later divided, in the frontal plane, into a dorsal rectum continuous with the midgut and a ventral urogenital sinus which receives the allantois.

The mouth.—The floor of the embryonic mouth or oral sinus is formed by the inner surfaces of the mandibular processes. The margins of its roof are formed laterally by the maxillary processes and anteriorly by the medial nasal process; and its central portion includes two membranous plates which separate the oral cavity from the *nasal pits* above. These plates soon disappear and the oral sinus communicates with the nasal chambers by paired *primitive choanæ* (fig. 38). The definitive palate is formed by the growth of the paired *palatine shelves* which arise from the medial borders of the maxillary processes and grow toward each other, fusing in the midline. In this manner the upper part of the original oral cavity is left above the palatine shelves, forming the inferior portions of the permanent nasal fossæ. The formation of the boundaries of the mouth has been considered in connection with the development of the face (p. 16). After their establishment they are invaded by ridges of oral epithelium which form the oral vestibule separating the lips and cheeks from the alveolar processes.

The teeth.—The teeth are formed in part from the oral ectoderm and in part from the mesoderm of the cores of the maxillary and mandibular arches. The ectodermal portion arises as vertical outgrowths from oral epithelium known as dental shelves, which extend into the alveolar processes and lie parallel with and medial to the labial grooves. A series of twenty cup-shaped expansions, the *enamel organs*, form on the free edges of the dental shelves. Each of these covers, in part, a small mass of condensed mesenchyma, the *dental papilla* (figs. 39 and 40).

Fig. 37.—Reconstructions of the Digestive Tract.

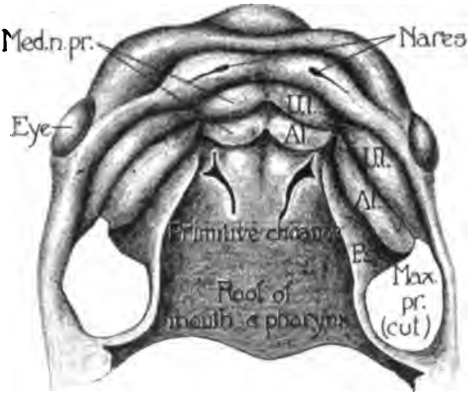
A, of an embryo 2.5 mm. long. (After Thompson and Lewis.) B, of an embryo 10 mm. long. (After Phisalix.)



The enamel organs enlarge rapidly and their connections with the dental shelves are reduced to slender necks. Each organ is differentiated into three parts: (1) a thin outer membrane attached by the neck to the dental shelf; (2) an inner membrane composed of a single layer of high columnar cells or ameloblasts; and (3) an intervening spongy mass, the enamel-pulp. Coincident with these changes the dental papilla is differentiated into a peripheral layer of olumnar cells or odontoblasts, which immediately underlies the inner layer of enamel organ, and a dense central core which is highly vascularized.

Fig. 38.—Reconstruction of the Oral Region of an Embryo of the Second Month. (From Schaeffer after Kollman and Keith.)

Al., alveolar processes. Max.pr., maxillary process. Med.n.pr., medial nasal process P.s., palatine shelves. U.l., upper lip.



The portion of the dental shelves which is not involved in the formation of the deciduous eeth gives rise to a second set of enamel-organs for the permanent dentition.

The *calcification* of the teeth begins in the eighteenth fetal week after the crowns are well outlined (fig. 40). The process starts at the crown of the tooth and extends toward the root. Simple teeth, such as the incisors, have single centers of calcification while teeth with two or more cusps have separate centers for each cusp, which soon fuse in a single mass. Calcification takes place in both the ectodermal and the mesodermal parts of the tooth germ. The cells of the inner layer of the enamel organ (ameloblasts) become greatly elongated and a deposit of enamel, in the form of fine globules, appears at their outer margins and gradually fills the cells, converting them into the *enamel-prisms*. The peripheral cells of the dental papilla (odontoblasts) likewise assume a columnar form and a deposit of dentine is laid down between them and the ameloblasts. As this material increases the odontoblasts retreat toward the center of the dental papilla, but processes which extend from them remain imbedded in the dentine as the dentinal fibers. The *cementum* which covers the dentine of the root is produced in connection with the surrounding mesenchyma in a manner similar to the formation of membrane-bone. The center of the dental papilla with its blood-vessels, lymphatics and nerves remains as the *pulp* of the tooth.

FIG. 39.—DIAGRAMS SHOWING THE EARLY DEVELOPMENT OF THREE TEETH. One is shown in vertical section. (After Lewis and Stöhr.)

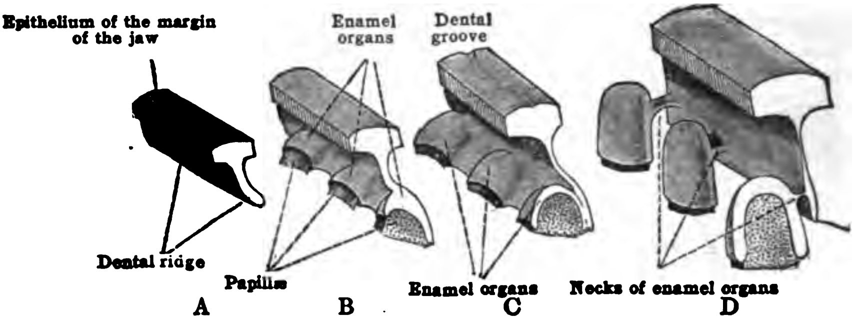
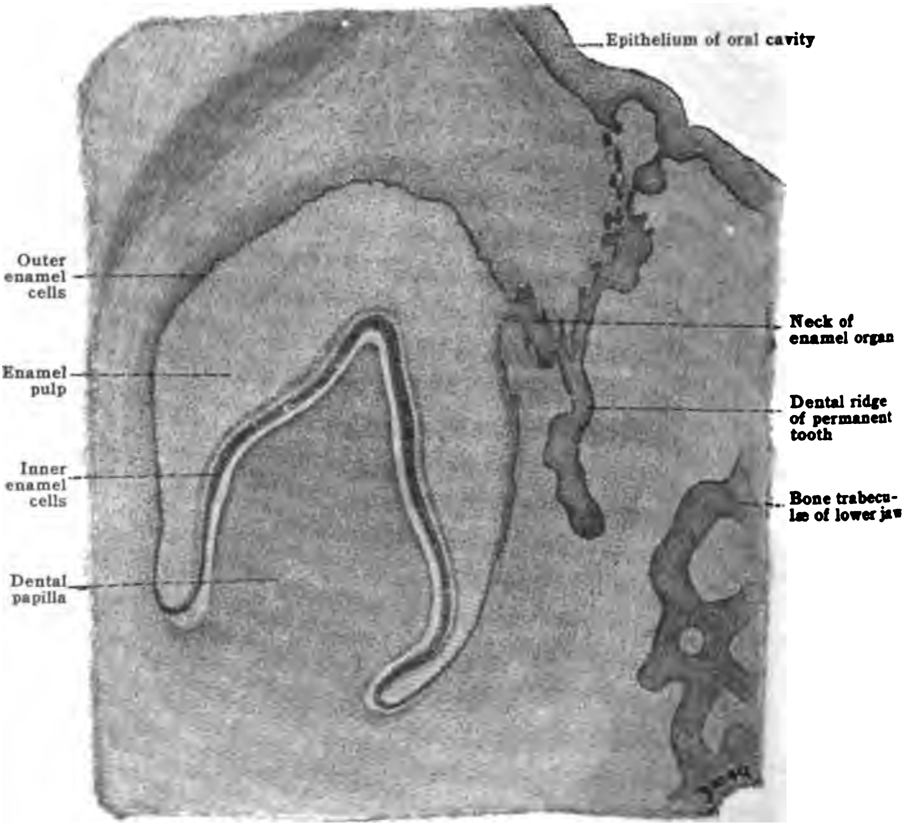


FIG. 40.—SECTION SHOWING LATER STAGES OF TOOTH DEVELOPMENT. (After Szymonowicz.)

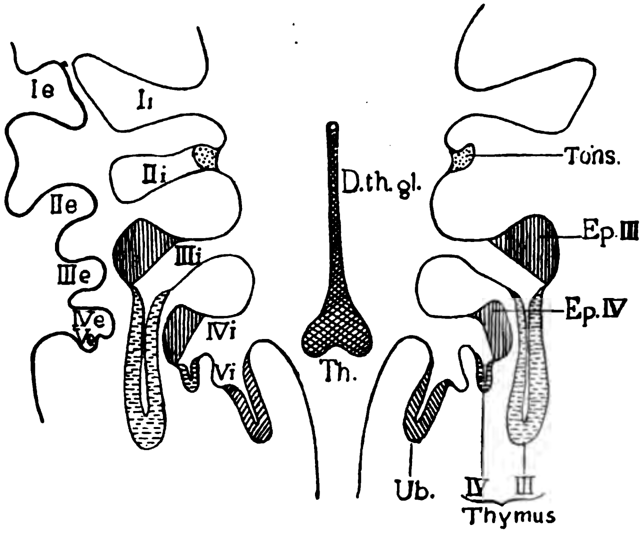

Epithelium of oral cavity
Outer enamel cells
Enamel pulp
Inner enamel cells
Dental papilla
Neck of enamel organ
Dental ridge of permanent tooth
Bone trabeculæ of lower jaw

At the time of birth the germs of all the deciduous teeth and of all the permanent teeth, except the second and third molars, are present, and those of the deciduous teeth and the first permanent molars are partially calcified. The germs of the second permanent molars are formed in the second postnatal month but those of the third molars do not appear until about the fifth year. The later history of the teeth, including the chronology of their eruption, is considered in connection with the digestive tract (p. 1154).

The tongue.—The anterior part of the tongue is formed from a pair of lateral lingual swellings which appear in the floor of the mouth, at the level of the first branchial arch, early in the second month. These fuse together medially, replacing an earlier median swelling in this region, the *tuberculum impar*. The posterior part of the tongue is formed from the medial portion of the second, and possibly the third, branchial arch. The *musculature* of the tongue arises in situ from the thickened mesenchyma of the lingual region but its innervation (by the hypoglossal nerve) as well as its comparative development indicate that it was originally derived from certain of the occipital somites. The epithelium of the tongue is probably partly of ectodermal and partly of entodermal origin, the terminal sulcus indicating the boundary between the two layers.

FIG. 41.—DIAGRAM TO SHOW THE DERIVATIVES OF THE BRANCHIAL POUCHES.

Ie, IIe, IIIe, IVe, Ve, external branchial grooves. Ii, IIi, IIIi, IVi, internal branchial pouches. Tons., palatine tonsil. EpIII, EpIV, parathyroid glands. Ub, ultimobranchial body. Th., thyroid gland. D.th.gl., ductus thyroglossus. (Modified from Keibel and Mall.)



The salivary glands.—The parotid gland is formed from a shelf-like outgrowth of the epithelium at the angle of the mouth between the maxillary and mandibular processes; and the submaxillary and sublingual glands are formed from similar outgrowths from the medial and lateral angles of the grooves between the tongue and lower alveolar processes. The general scheme of the later development of submaxillary and parotid glands and the major portion of the sublingual gland is much the same. Each grows backward as a keel-like flange which becomes detached from the oral epithelium except for a small anterior connection which represents the future ostium of the duct of the gland. The proximal portion of the outgrowth forms the main duct of the gland, the distal expanded portion giving rise, by repeated divisions, to the smaller ducts and alveoli. The minor sublingual mass is developed from a series of separate outgrowths.

The pharynx.—The pharynx forms a considerable portion of the digestive tube in the young embryo. Its relative size undergoes a marked decrease in fetal life, followed by a slower reduction after birth. During infancy and childhood the length of the pharynx increases rapidly while the anteroposterior diameter grows slowly and the width remains almost unchanged. All diameters increase in middle and later childhood but the growth in length is still the most rapid. In adolescence there is a limited growth of all diameters.

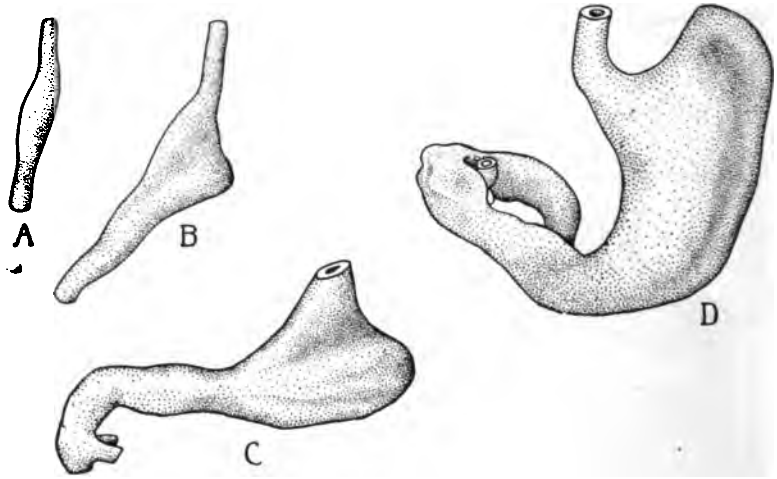
During the fourth week four pairs of *branchial* (*pharyngeal*) *pouches* are formed from the lateral walls of the pharynx and a single median outgrowth (the thyroid diverticulum) appears in its floor. The pharyngeal pouches correspond in position to the branchial grooves, which are formed on the external surface of the neck, and are separated by the branchial arches. They give rise to a number of structures which are quite dissociated in later life (figs. 41 and 56).

The *first pouch* is directed dorsally and laterally. Its outer extremity is expanded forming the tympanic cavity of the middle ear, while its proximal part is converted into the auditory (Eustachian) tube. A dorsal recess from the *second pouch* forms the tonsillar sinus and the epithelial portion of the palatine tonsil. The histories of the *third* and *fourth pouches* are similar. Both form dorsal and ventral diverticula, the former giving rise to the parenchyma of the parathyroid glands and the latter to the reticulum and thymic (Hassal's) corpuscles of the thymus. The stalks of these pouches merge in the piriform recess. A pair of small *ultimobranchial bodies*, which possibly represent a fifth pair of pouches, arise from the lateral walls of the pharynx behind the fourth pouches. They form epithelial masses which migrate into the cervical region and are intimately associated with the thyroid. It is improbable that they form any part of this structure but they may give rise to small epithelial masses known as the *glandula insularis cervicalis*.

The palatine tonsils.—About the fourth fetal month solid epithelial buds from the floor of the second pouch invade the surrounding connective tissue. These are later converted into the fossulæ and glands of the palatine tonsil. Lymphoid cells are found in the mesenchymal tissue under the tonsillar epithelium in the sixth fetal month, but definite lymphoid nodules are not present until nearly the time of birth. The postnatal growth of the palatine tonsil is extremely variable. In many cases they reach their highest development in the fifth or sixth year and involution takes place in later childhood. Apparently, in other instances, their growth may continue to puberty or early adolescence. Early in the third fetal month the *plica triangularis* arises from the floor of the pharynx opposite the second pouch and grows upward over a portion of the tonsillar sinus. At the time of birth the plica triangularis forms a fold which surrounds the tonsil, except for a small portion of its posterior border, and covers a part of its free surface. The fusion of the plica triangularis with the walls of the tonsillar sinus is already under way at this time and many specimens show the characteristic subdivisions of the cavity which are found in the adult. In later fetal life and at birth the tonsil lies somewhat higher in the sinus than in later life and its axis is horizontal. The tonsil descends during infancy and its longer axis becomes vertical.

Fig. 42.—Development of the Stomach.

A, embryo 5 mm. long. B, embryo 8 mm. long (after Broman). C, embryo 10 mm. long. D, embryo 19 mm. long (after Lewis).



The pharyngeal tonsil and bursa.—Early in the second fetal month there appears in the roof of the pharynx a small pouch, the *pharyngeal bursa*, from which there develop a series of radiating folds which extend anteriorly nearly to the nasal openings. In the later fetal months these are invaded by lymphoid tissue and are converted into the *pharyngeal tonsil*. The structure reaches its maximum development in early childhood. Its involution generally begins in the prepuberal period and is completed in early adolescence. The bursa pharyngea is commonly converted into a small closed cyst which remains throughout adult life.

The esophagus.—The esophagus in young embryos is a short tube of relatively large caliber, flattened from side to side. During the early part of the second month it becomes considerably elongated but is reduced in relative diameter and assumes a cylindrical form. At birth the tube is 8 to 10 cm. (3 to 4 in.) in length from the cricoid cartilage to the cardia. Its length is doubled in the first three years and tripled by puberty, but there seems to be little longitudinal growth thereafter.

The stomach.—The stomach appears in the fourth week as a spindle-shaped enlargement of the lower part of the foregut. This is soon subdivided by the *incisura angularis* (or gastric angle) into an upper expanded cardiac and a lower tubular pyloric portion (fig. 42). The fundus develops as an outpouching of the cardiac portion in the latter part of the second month and the gastric canal ('Magenstrasse') is established about the same time. A little later the pyloric portion is subdivided into pyloric canal and antrum. As these changes take place the stomach is bent to the right at the level of the incisura angularis, and the entire organ is rotated from left to right through about 90 degrees. After this time the stomach changes little in form until distended by its contents, either before or immediately after birth, when there is a considerable expansion of the fundus, body and greater curvature.

In early stages, the long axis of the stomach is vertical. With the establishment of the incisura angularis it often becomes transverse or oblique but it commonly returns to the vertical position in late fetal life. With the distension which occurs at birth the long axis again becomes obliquely transverse and this position is usual until the erect posture is habitually assumed,

Figs. 43, 44, 45, 46, 47 and 48.—A Series of Reconstructions and Dissections Illustrating the Growth and Topography of the Viscera in the Developmental Period. All specimens drawn to the same crown-rump length.

Fig. 43, embryo 4.2 mm. long. (Modified from His.) Fig. 44, embryo 11 mm. long. (Modified from Jackson.) Fig. 45, embryo 17 mm. long. (Modified from Jackson.) Fig. 46, fetus 65 mm. long. (Modified from Jackson.) Fig. 47, newborn 51 cm. long. Fig. 48, adolescent. (Based on drawings and casts of His and Symington.) Nervous system, yellow; gastro-intestinal tract, red; spleen, blue; Wolffian body, green. All., allantois. Ao., aorta. Bl., bladder. Cl., cloaca. C.V., cardinal veins. E., esophagus. G., genital gland. Ht., heart. I., intestine. K., kidney. L., liver. Lg., lung. Ph., pharynx. Sr., suprarenal gland. St., stomach. U., uterus. W. b., Wolffian body.

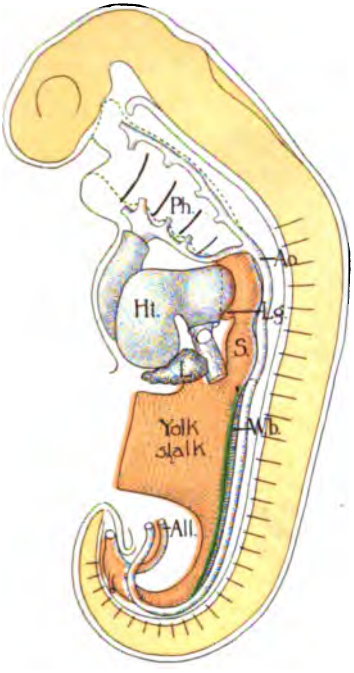


Fig. 43.

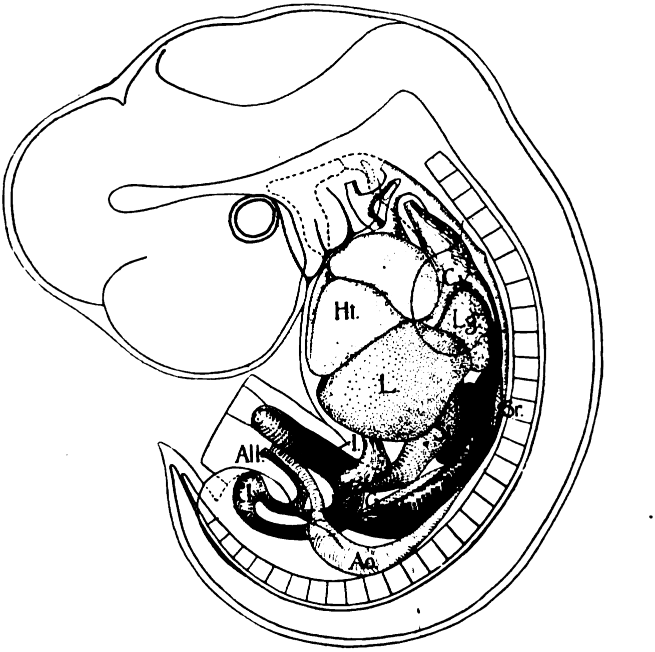


Fig. 44.

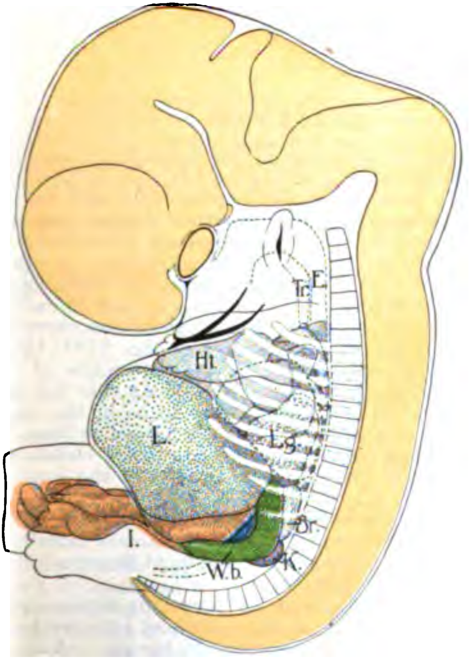


Fig. 45.

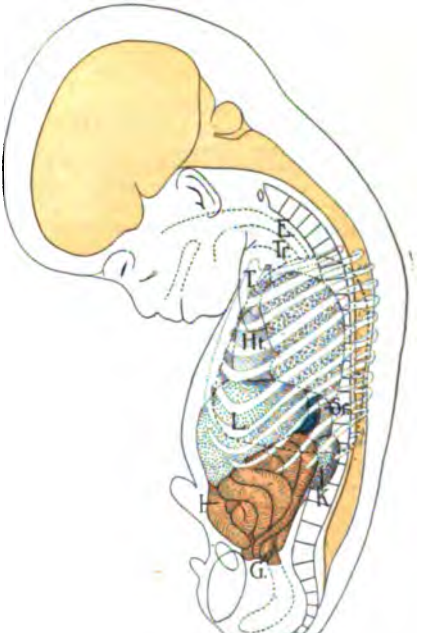


Fig. 46.

when the vertical position again becomes the more common. At the time of its differentiation the stomach lies in the upper part of the thorax but in early fetal life it descends to the upper abdominal region. There is little later change in the positions of the orifices of the stomach but with its subsequent growth in size and changes in form the lower margin gradually descends in the abdomen during the greater part of childhood.

The stomach grows with great rapidity in the latter part of fetal life and this rate is continued in the first trimester of postnatal life. The stomach increases in weight about 24 times between birth and maturity, its postnatal growth following the course of the splanchnic group of organs. The capacity of the stomach at birth is about 30 cc. It rises rapidly to about 90 or 100 cc. at the end of the first month and thereafter increases more slowly to 250 to 300 cc. at the end of the first year.

The development of the intestines.—With the separation of the archenteron from the yolk-sac the intestinal tract is established as a short and relatively straight tube extending from the stomach swelling to the cloaca. This tube in its rapid elongation is thrown into three main or primary loops and a number of secondary ones. The primary loops are: (1) the gastroduodenal loop which forms the upper portion of the duodenum; (2) the enterocolic or umbilical loop which gives rise to the distal portion of the duodeum, the jejunoileum, and the cecum, ascending colon and a part of the transverse colon; and (3) the left colic loop which forms the remainder of the large intestine. The gastroduodenal loop is short and simple needing no further description. The umbilical loop first lies in the median sagittal plane of the body. It consists of a cranial and a caudal limb and a yolk-stalk arises from its summit which projects into an extension of the body-cavity, the umbilical celom. A slight swelling on the caudal limb marks the position of the cecum and the division between small and large intestines. In its further growth the umbilical loop turns on its axis and its caudal limb is carried first to the left, then anteriorly and later to the right of the proximal one, carrying the cecum with it. The development of the coils of the small intestine (see page 1194) takes place partly in the abdominal and partly in the umbilical celom. During the middle of the fourth month they return rather suddenly to the abdominal cavity and following this the first part of the colon and the cecum pass ventrally over the small intestines to lie in the right hypochondriac region below the liver. Later the cecum descends into the right iliac fossa to a level a little below that occupied in the adult. Its final position is acquired in early childhood after a slight ascent which is probably associated with the postnatal growth of the lumbar region.

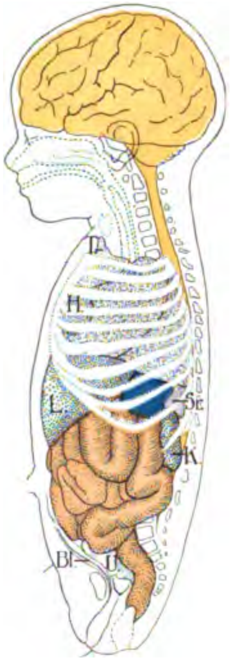


FIG. 47.

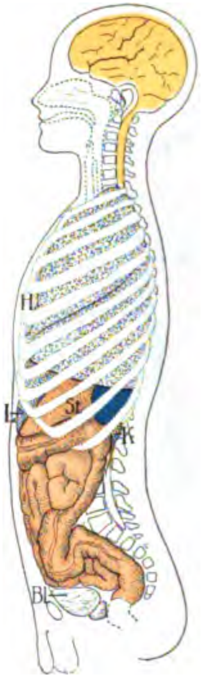


FIG. 48.

The left colic loop is formed by the bending of the lower part of the intestinal tube to the left side of the abdominal cavity some time after the formation of the other primary intestinal loops. Secondary curves in this loop form the left colic (splenic) and sigmoid flexures. For further details on the development of the intestines, see p. 1204.

The cecum and vermiform process (appendix).—The formation of the swelling which represents the cecum was mentioned above. After the rotation of the umbilical loop the cecal swelling is extended as finger-like projection from the ventral surface of the gut. A small diverticulum which represents the vermiform process arises from the apex of this projection in the third fetal month (fig. 50). The vermiform process grows rapidly, reaching its full relative length (as compared to the length of the intestine) by the middle of fetal life. In the fourth month the cecal projection is bent at right angles to the main axis of the segment of the intestine from which it arises and the ileocecal valve is formed by invagination of the terminal portion of the walls of the ileum at this point. At birth the cecum is relatively small. Its lower end becomes directly continuous with the vermiform process without a sharp line of demarcation and the cecal sacculations are generally absent. The appendix usually lies directly below the cecum at this time, or is bent upward at an acute angle along its medial margin. The development of the cecal sacculations and the formation of a distinct cecal fundus usually takes place in early childhood (generally in the third or fourth year).

FIG. 49.—DISSECTION OF THE THORACIC AND ABDOMINAL VISCERA OF A FETUS OF THE FIFTH MONTH.

C., cecum. Cl., colon. Ht., heart. K., kidney. L., lungs. Sp., spleen. Sr., suprarenal gland. St., stomach. U., umbilicus. Ov., ovary.

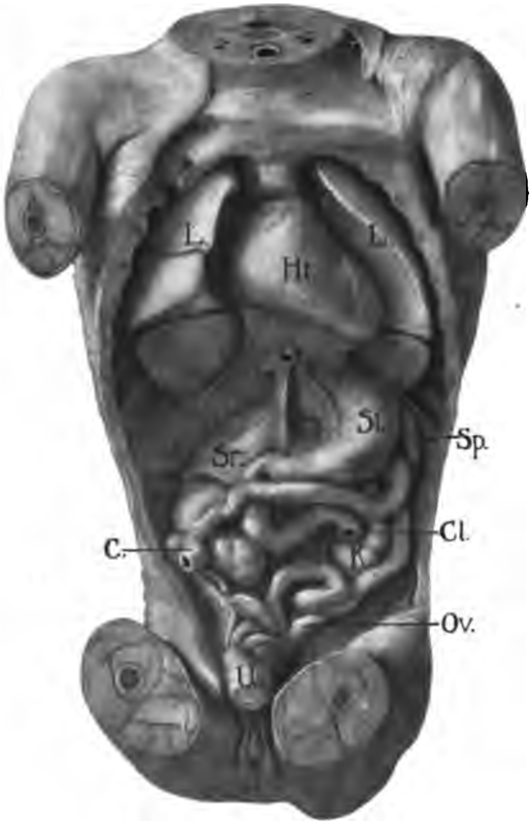
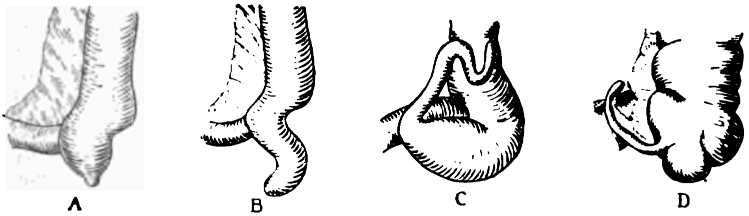


FIG. 50.—FOUR STAGES IN THE DEVELOPMENT OF THE CECUM AND VERMIFORM PROCESS. (After Kollmann and Paterson.)

A, embryo at the end of the second month. B, fetus of the third month. C, child ten weeks after birth. D, child of 5 years.

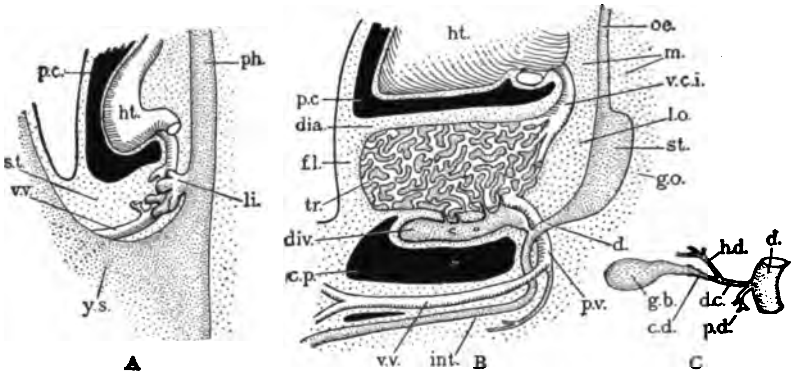


The rectum and anal canal.—The rectum is formed from the dorsal portion of the cloaca which is separated from the urogenital sinus by the formation of the urorectal septum. At the same time the posterior part of the cloacal membrane is separated from the anterior portion and forms the *anal plate* which is later invaginated forming the anal canal. The rectum and anal canal are separated until comparatively late in the development by the *anal membrane* which lies at the level of the future anal valves. A want of rupture of the anal membrane is known as congenital atresia of the anus.

Growth of the intestines.—The growth of the intestines in the early part of prenatal life is very rapid. At birth they form about 1.5 per cent. of the body as compared with 0.75 per cent. in maturity. The absolute length of the intestines at birth is usually between 350 and 400 cm. (12 to 14 feet). The intestinal tract grows about 50 per cent. in length in the first year. Thereafter the increase is much slower, the length in the adult being about 2.5 times that of the newborn.

Fig. 51.—Diagrams of the Development of the Liver. (After Lewis.)

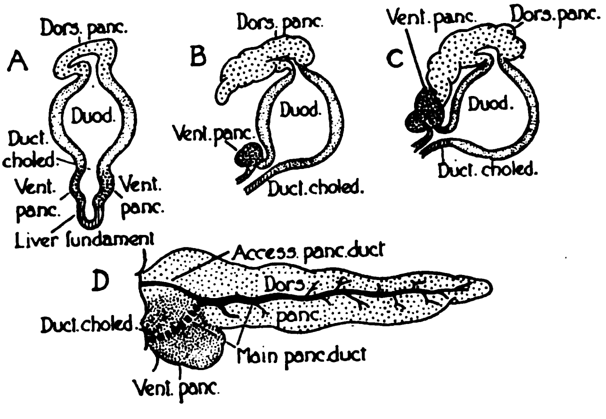
A, the condition in a 4.0 mm. human embryo. B, a 12 mm. pig. C, the arrangement of ducts in the human adult. c.d., cystic duct. c.p., cavity of the peritoneum. d., duodenum. d.c., ductus choledochus. dia., diaphragm. div., diverticulum. f.l., falciform ligament. g.b., gall-bladder. g.o., greater omentum. h.d., hepatic duct. ht., heart. int., intestine. li., liver. l.o., lesser omentum. m., mediastinum. oe., esophagus. p.c., pericardial cavity. p.d., pancreatic duct. ph., pharynx. p.v., portal vein. st., stomach. tr., trabecula. v.c.i., vena cava inferior. v.v., vitelline vein. y.s., yolk-sac.



In the early part of the embryonic period the large intestine forms nearly one-half of the length of the intestinal tract. But by the fourth fetal month it is reduced to about one-fifth of the total length of the intestines and this ratio is maintained throughout the remainder of life, except for a period of increase in the length of the colon in the latter fetal months due to its distension by meconium.

The liver.—The liver arises in the third week as a thickened area in the floor of the posterior part of the foregut (figs. 37A, 43, 51, 62). This area forms a small, thick-walled pouch in which may be recognized an anterior hepatic and a posterior cystic portion. The cystic part forms the common bile-duct, the gall-bladder and cystic duct, and probably the main hepatic ducts. The hepatic portion gives rise to a large number of cellular cords which anastomose freely interdigitate with the neighboring veins, and form the parenchyma of the liver. Certain of these cords, which lie close to the developing portal veins, form the minor hepatic ducts. For further details on the development of the liver, see p. 1215 and figs. 918, 963.

Fig. 52.—A, B, C, Diagrams Illustrating the Development of the Pancreas. (After Laguesse.) D, Diagram Illustrating the Embryonic Constituents of the Adult Pancreas. (After Charpy.)



The liver grows with great rapidity in the embryonic period forming over 7 per cent. of the body in the second and third fetal months. After this time the relative weight declines to about 4 per cent. at birth, 3 per cent. in childhood and 2.5 per cent. in maturity. The postnatal growth of the liver in absolute weight follows the general course of the splanchnic viscera and the total increase between birth and maturity is about 13-fold. In fetal life the gall-bladder is small in proportion to the liver, being more or less buried in its substance, but it grows rapidly in infancy and the adult relation between these structures is established by the end of the second year.

The pancreas.—The pancreas (fig. 52) arises in the fourth week from two thickenings of the wall of the posterior part of the foregut.. The first of these to appear is the dorsal pancreas which is formed from the roof of the primitive duodenum caudal to the fundament of the stomach. The second or ventral pancreas, which is sometimes a paired structure, arises from the floor of the gut at the cephalic end of the liver-pouch. Both diverticula differentiate into proximal stalks and distal expanded portions, the former forming the main ducts of the gland and the latter giving rise to the minor ducts and alveoli. Both pancreatic diverticula turn to the right in their growth and, passing around the right side of the intestine, come in contact near the point of origin of the ventral pancreas. Later, in connection with the rotation of the intestinal tube, the pancreas is shifted to the left of the duodenum. A fusion of the two elements takes place through the anastomosis of their main ducts. In later life the ventral pancreas is represented by the proximal portion of the main pancreatic duct and the lower part of the head of the pancreas. The remainder of the parenchyma of the gland, the accessory pancreatic duct (when present) and the distal portion of the main duct are derived from the dorsal pancreas. The relation of the pancreas to the primitive mesentery is shown in figs. 918 and 966.

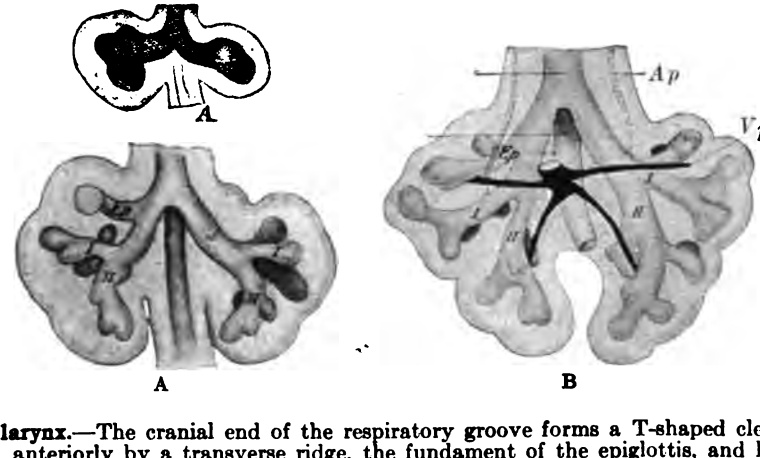
The pancreas grows relatively slowly until the sixth fetal month when it enters on a period of more rapid growth which extends well into the first year of postnatal life. The organ increases in weight nearly 30 times in postnatal life. Its general course of growth is that of the splanchnic group of viscera.

THE RESPIRATORY SYSTEM

Early development of the respiratory system.—The entodermal fundament of the respiratory system arises in the third week as a median groove in the hind part of the floor of the pharynx. The cranial portion of this groove, which represents the larynx, remains attached to the pharynx while the caudal portion grows downward as a respiratory bud which represents the trachea and the lungs (figs. 37B, 43). The free end of the respiratory bud is expanded into a rounded vesicle which immediately bifurcates into right and left branches or lung-buds.

FIG. 53.—RECONSTRUCTION OF THE LUNG OUTGROWTHS OF EMBRYOS OF (*A*) 4.3, (*B*) 8.5., AND (*C*) 10.5 MM.

Ap, Pulmonary artery; Ep, eparterial bronchus; Vp, pulmonary vein; I, second lateral bronches; II, main bronchi.—(His.)



A B

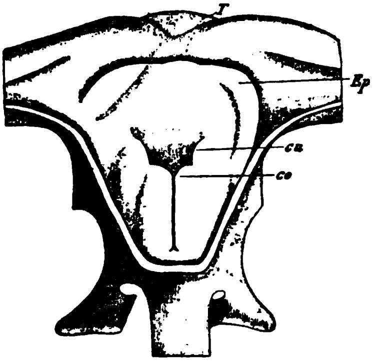
The larynx.—The cranial end of the respiratory groove forms a T-shaped cleft which is bounded anteriorly by a transverse ridge, the fundament of the epiglottis, and laterally by paired arytenoid swellings which represent the cuneiform and corniculate tubercles and the aryepiglottic folds. The epithelial surfaces of the arytenoid swellings soon fuse, forming a plate which obliterates the upper part of the respiratory groove. The cavity of the larynx is reestablished in the second month by the disintegration of the central cells of this plate. The ventricle and ventricular and vocal folds are formed by lateral extensions of the laryngeal cavity in this region.

The **laryngeal cartilages** are differentiated in the mesenchyma surrounding the epithelial tube of the larynx. Their chondrification begins in the second fetal month but is not completed until shortly before birth. The derivation of the thyroid cartilage is considered in connection with the development of the branchial skeleton (p. 29).

The larynx is relatively large in the fetus and newborn. At birth the absolute vertical dimensions are a little less and the transverse dimensions a little more than one-third those of the adult (fig. 55). Three phases can be recognized in the postnatal growth of the larynx: (1) a period of general rapid growth from birth to 2 or 3 years: (2) a succeeding period to prepuberty in which growth proceeds rather slowly although there are some alterations in form: and (3) a second period of rapid growth (most noticeable in males) in later childhood and adolescence. Sexual differences are said to appear in the larynx in the third year and after this time the male larynx is larger than the female. The larynx gradually descends in the neck during the fetal period and childhood.

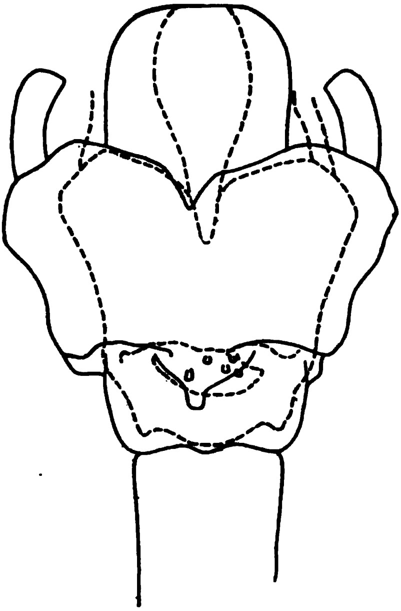
The trachea.—The trachea is formed from the portion of the respiratory bud lying between the laryngeal groove and the lung-buds. The tracheal cartilages and musculature develop in the second month from the mesenchyma surrounding the tube, and the tracheal glands first appear towards the close of the third month. The length of the trachea is nearly tripled between birth and maturity. The diameter of the trachea increases 4 or 5-fold after birth.

Fig. 54.—Reconstruction of the Opening into the Larynx in an Embryo of Twenty-eight Days. Seen from behind and above, the dorsal wall of the pharynx being cut away. (From McMurrich after Kallius.) co, Cornicular, and cu, cuneiform tubercle. Ep, epiglottis. T, unpaired portion of the tongue.



The lungs.—The lining of the bronchial tree and the alveoli (air-cells) of the lungs is formed by the repeated division of the lung-buds and their branches (fig. 53). While the terminal branches of the bronchial tree arise from the larger stems by typical dichotomous division the main trunks are formed by monopodial division, straight or but slightly curved while the smaller arise as side branches from them. From an early stage the lung-buds are asymmetrical, the right being larger than the left and directed more caudally. The early branching of the buds is also dissimilar, the right bud forming two side buds (representing the bronchial ram or the upper and middle lobes), the left bud forming but one (representing the bronchus of the upper lobe).

Fig. 55.—Outline Drawings of the Larynges of an Adult and a Newborn. Reduced to the same size and superimposed, showing the differences in proportions at birth and in maturity. Adult in dotted line; newborn in solid line.



The formation of alveoli from the tips of the terminal branches of the bronchial tree begins in the sixth fetal month. Their number grows rapidly but they increase little in size before birth. At birth, with the establishment of respiration the alveoli expand vigorously their lining epithelium being reduced from a columnar to a squamous type. Aside from the possible growth of a few air-cells from the walls of the terminal bronchioles there are no new alveoli formed after birth. The size of the alveoli, however, continues to increase throughout life, even to extreme old age.

The visceral *pleura* is formed from the splanchnic mesoderm of the parietal part of the celom which carries the lung-buds as they push their way into this cavity, and the stroma of the lung is probably derived from cells of this layer. The connective tissue of the lung is extremely abundant in the early part of the fetal period but the relative amount is greatly reduced in the last fetal months by the increase in the number of alveoli and still more so by the expansion of the alveoli at birth.

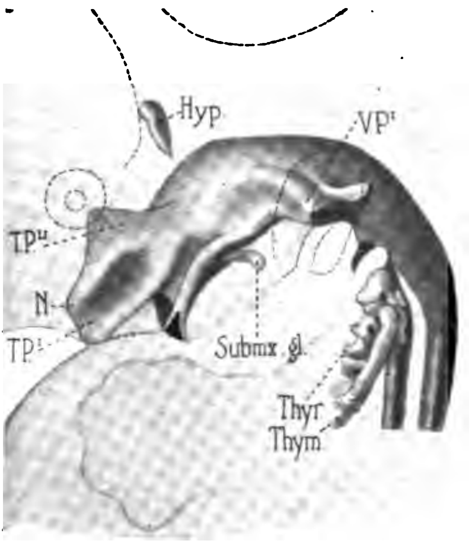
The lungs are formed in the upper cervical region but in their development they descend at first rapidly and then more slowly into the thoracic cavity. There is little change in the position of the lungs in infancy but a slow descent in childhood.

The lungs reach their highest relative weight in the fourth fetal month when they form about 3.3 per cent. of the body. In the newborn they form about 1.7 to 2.0 per cent. and in the adult about 1 per cent. of the body-weight. The growth of the lungs in absolute weight during postnatal life follows the scheme of the splanchnic group of organs.

The nose and paranasal sinuses.—The formation of the nasal pits, development of the external nose, and establishment of the hard palate have already been considered (p. 38). In the early part of the second month the nasal fossæ are represented by the two nasal pits which open to the surface of the face through the embryonic nares (fig. 17) and are separated medially by the primitive nasal septum. They communicate with the oral sinus through the primitive choanæ (fig. 38).

FIG. 56.—LATERAL VIEW OF A MODEL OF THE NOSE AND PHARYNX OF AN EMBRYO OF 6 WEEKS. (After Sudler.)

Hyp., anterior lobe of the hypophysis. N., nasal cavity. Submx.gl., submaxillary gland. Thym., thymus. Thyr., thyroid. T.P^{1},. inferior concha. T.P^{2},. middle concha. V.P., first branchial (pharyngeal) pouch.



The floor of the definitive nasal fossæ is formed by the fusion of the palatine shelves of the maxillary processes. During this change the primitive choanæ are merged in the nasal fossæ and the definitive choanæ are formed, eventually assuming their final position between the posterior ends of the nasal fossæ and the nasopharynx. At the same time the lower parts of the nasal fossæ are completely separated by the union of the lower margin of the nasal septum with the upper surface of the fused palatine shelves (fig. 38).

The agger nasi and inferior concha arise as processes from the lateral walls of the nasal fossa and the conchæ above them from both the medial and lateral walls of the upper parts of the fossæ. The conchæ are developed in part by the actual outgrowth of shelves from the wall and in part by the formation of grooves which limit these processes. The formation of the conchæ begins in the seventh week. For further details on the development of the nose, see p. 1238.

When the definitive nasal fossæ are first established they are quite short anteroposteriorly but their height and breadth are relatively great. During fetal life the length of the chambers grows more rapidly than the height and at birth the fossæ are relatively long, broad and low. The height of the fossæ increases nearly one-half in infancy but grows much more slowly thereafter. At 7 years it is about twice and in the adult 2.5 to 3 times as great as in the newborn. Apparently the length of the nasal fossæ is about doubled in the first decade and increases little thereafter. The breadth of the nasal cavity, on the other hand, increases very slowly in early childhood.

The *paranasal sinuses* arise as evaginations of the nasal mucous membrane in the latter part of the third and in the fourth fetal months. Their subsequent history is considered in connection with their adult anatomy (p. 1238).

THE UROGENITAL SYSTEM

All three germ-layers are involved in the formation of the urogenital system. The mesodermic contribution is derived from the intermediate mesoderm, the entodermal from the caudal ends of the cloaca and allantois, and the ectodermal mainly from the cloacal membrane.

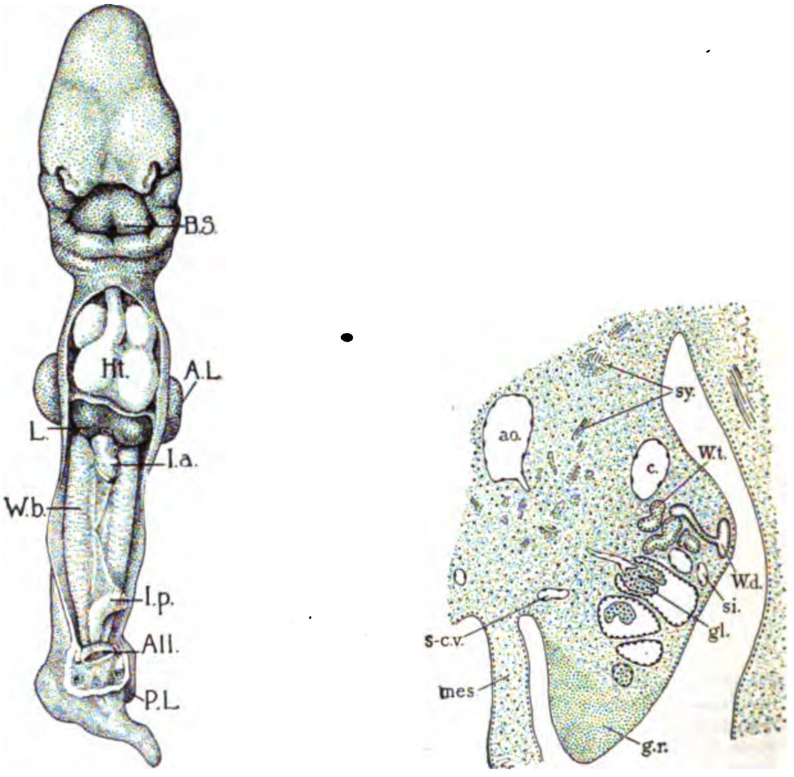
The excretory portion of the urogenital system is derived entirely from the intermediate mesoderm. In man, as well as in other mammals, and in reptiles and birds, there are formed successively in the embryo three sets of excretory organs or kidneys. The first of these, the pronephros or head-kidney, is a rudimentary structure even in the embryo and disappears completely except for its duct. The second, the mesonephros or Wolffian body, becomes a functional excretory organ in the embryo, but later degenerates with the exception of certain portions which are retained as parts of the male genital system and others which remain as vestigial structures. The third, the metanephros, remains as the permanent kidney.

FIG. 57.—A, DISSECTION OF AN EMBRYO OF THE FIFTH WEEK, SHOWING THE WOLFFIAN BODY. (After Coste.)

A.L., anterior limb-bud. All., allantois. B.S., buccal sinus. Ht., heart. I.a., cranial limb of umbilical loop of the intestine. I.p., caudal limb of umbilical loop of the intestine. P.L., posterior limb-bud. W.B., Wolffian body.

B, TRANSVERSE SECTION OF THE WOLFFIAN BODY OF A HUMAN EMBRYO 10 MM. LONG. (After Lewis.)

ao., aorta. c., posterior cardinal vein. gl., glomerulus of Wolffian tubule. g.r., genital ridge. mes., mesentery. s.c.v., subcardinal vein. si., sinusoid. sy., sympathetic nerves. W.d., Wolffian duct. W.t., Wolffian tubule.



A

B

The pronephros.—The pronephros arises as a series of outgrowths from the intermediate cell-mass of the cervical region. These sprouts develop into tubules which connect medially with the body-cavity and end blindly laterally. The blind ends of the tubules are directed caudally and growing backward fuse with one another forming a solid cord. The pronephros is a transitory structure and by the fifth week all of its tubules have degenerated; but the longitudinal cord formed from them persists, acquires a lumen, and, growing backward, connects with the lateral wall of the cloaca. It is now called the Wolffian duct.

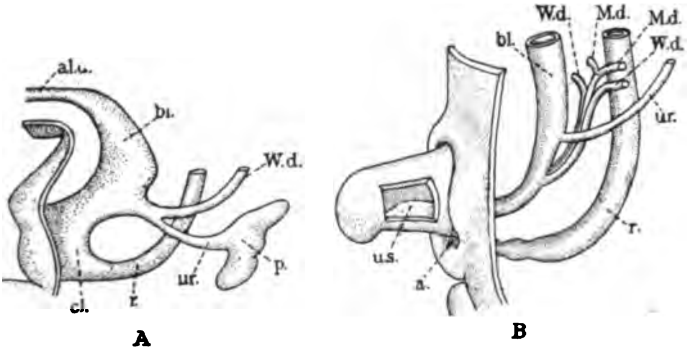
The mesonephros and the Müllerian ducts.—The mesonephros arises as a series of tubules from the intermediate mesoderm of the lower cervical, thoracic, and the greater part of the lumbar region. These tubules become disconnected from the intermediate cell-mass, their lateral ends joining the Wolffian duct while their medial extremities are expanded into cup-shaped vesicles which enclose a capillary tuft derived from arterial sprigs which pass to them from the aorta. When fully developed the Wolffian or mesonephric tubules form a pair of large masses projecting from the dorsal wall of the abdominal cavity on either side of the mesentery (figs. 43–45, 57A). These masses, the Wolffian bodies, reach their greatest development in the sixth or seventh week and thereafter undergo a rapid involution, except for certain parts which are retained in connection with the genital glands.

At the time when the Wolffian body has almost reached its highest development the peritoneum near its cranial end on the medial surface is invaginated forming a second longitudinal duct, the Müllerian duct, which lies parallel with the Wolffian duct. The Müllerian ducts grow posteriorly and join the urogenital sinus. In the lower part of their course the Müllerian ducts lie side by side. They subsequently fuse into a single tube in this region and open into the urogenital sinus through a single ostium. Their upper parts, which are associated with the Wolffian bodies, remain paired and separate.

The metanephros.—The metanephros or permanent kidney is formed from the metanephric bud (primitive ureter), which is an outgrowth from the Wolffian duct, and from a thickened mass of mesenchyma, the metanephric blastema, derived from the lower part of the intermediate mesoderm. The metanephric bud arises from the lower part of the Wolffian duct in the fourth week. It grows backward and upward behind the Wolffian body where its distal end encounters and becomes imbedded in the metanephric blastema. The distal end forms the renal pelvis while the proximal portion remains as the ureter. The renal tubules are formed in part from the renal pelvis and in part from the metanephric blastema, the former giving rise to the straight and arched collecting segments and the latter to the remainder of the tubule. The metanephric blastema also forms the stroma of the kidney. The renal tubules are formed in a series of 14 to 18 generations, the last formed tubules occupying the periphery of the kidney. All of the renal tubules have been formed at birth and the subsequent increase in the renal parenchyma (about 90 per cent. of the total growth) takes place entirely through tubule hypertrophy.

Fig. ,58.—Development of the Urogenital Sinus. (From Lewis after Keibel.)

A, embryo 11.5 mm. long (4½ weeks). B, embryo 25 mm. long (8½ to 9 weeks). a, anus. al.d., allantoic duct. bl., bladder. cl., cloaca. M.d., Müllerian duct. p., pelvis of kidney. r., rectum. ur., ureter. u.s., urogenital sinus. W.d., Wolffian duct.



The position of the kidneys changes greatly during development. Starting in the sacral region they gradually pass into the abdominal region in the second month. In later fetal life they are shifted downward so that their lower poles are usually in the pelvis at the time of birth, but in infancy there is commonly a second upward shifting of the kidneys. The later changes in the position of the kidneys are probably passive, dependent on the growth of the posterior wall of the trunk.

The kidneys form about 0.7 per cent. of the weight of the body at birth. They decrease to about 0.46 per cent. in maturity, their total postnatal increase being about 14-fold. Their growth in absolute weight follows the general course of the splanchnic group of organs.

The urogenital sinus.—In young embryos the hindgut and the allantois unite in a common cloaca. This chamber is joined on either side by the Wolffian ducts and its ventral wall is formed, in part, by the cloacal membrane. The cloaca becomes divided, in the frontal plane, by the rectourethral septum into a dorsal (posterior) rectum and a ventral (anterior) urogenital sinus. This partition extends to the cloacal membrane which is differentiated into a ventral portion, associated with the later development of the urogenital sinus and a dorsal (posterior) part which forms the anal canal (see p. 38). The Wolffian ducts remain connected with the urogenital sinus when the cloaca is divided, and the ureters which spring from the Wolffian ducts separate from them and acquire independent openings in the urogenital sinus cranial to the ostia of the Wolffian ducts. At this time also the Müllerian ducts form a connection with the sinus medial to the openings of the Wolffian ducts.

The urogenital sinus is later differentiated into three segments. The upper portion (pars vesicalis) is an expanded chamber receiving the ureters and continuous with the allantois cranially. The middle portion (pars urethralis) is a short tube into which the Müllerian and Wolffian ducts open. The lower segment (pars phallica) is widely expanded and is floored by he ventral portion of the cloacal membrane.

The *pars vesicalis* forms the bladder. Its lining epithelium is of entodermal origin except n the region of the future trigone which is derived from the mesoderm of the proximal ends of he ureters. The connection of the allantois with the bladder is lost in the second fetal month and the cranial third of the bladder is obliterated in fetal life, remaining as a fibrous band, the urachus. At birth the bladder is mainly an abdominal organ, its base lying behind the symphysis pubis and its apex extending halfway to the umbilicus, the long axis of the contracted organ being almost vertical at this time. During postnatal life the bladder shifts backward and downward in the pelvis. Three stages can be recognized in this process; a period of rapid descent in infancy and early childhood, a stationary phase in middle and later childhood, and a final period of slow descent in adolescence.

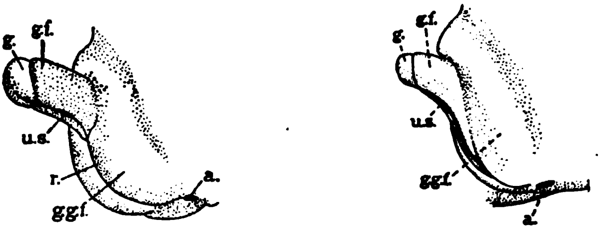
The *pars urethralis* forms the entire urethra in the female and the proximal portion of the urethra in the male. In the third fetal month the pars urethralis gives rise to a series of longitudinal folds from which are formed the prostatic tubules of the male and the corresponding but rudimentary paraurethral (Skene's) glands of the female. All of the prostatic glands are formed by the middle of fetal life.

The *pars phallica* enlarges in the second fetal month, encroaching on the pars urethralis and forming a shallow vestibule into which the urethra and the Müllerian ducts open independently. In its further development (which is considered in connection with external genitalia) the pars phallica is converted into the distal part of the urethra in the male and the vestibule in the female. A pair of evaginations from the lower part of the pars phallica in the fourth fetal month gives rise to the bulbovestibular glands in the female and to the bulbourethral glands in the male.

The external genitalia.—The formation of the external genitalia takes place through the development and transformation of a series of external elevations at the margins of the cloacal membrane. Each of these structures consists of a central core of mesenchyma covered by an outer layer of the ectoderm of the perineal region. A median elevation, the cloacal tubercle, is formed at the anterior end of the cloacal membrane in the fifth or sixth week. This is differentiated into an apical phallus, the genital eminence, and a basal portion, the genital tubercle, which surrounds the root of the phallus and extends caudally on either side of the cloacal membrane as the paired genital swellings. At the same time, the cloacal membrane forms a deep urethral groove the lips of which are converted into a second pair of longitudinal ridges termed the genital folds, which lie medial to the genital swellings. The urethral groove between them is converted into a longitudinal slit which connects the vestibule of the urogenital sinus with the exterior.

FIG. 59.—DIAGRAMS OF THE EXTERNAL GENITAL ORGANS. (A) of a male embryo. (B) of a female embryo. (After Lewis.)

a., anus. g., glans clitoridis and glans penis. g.f., genital folds. g.g.f., genital swellings. r., raphe. u.s., urogenital sinus.



In the female the phallic part of the cloacal tubercle forms the clitoris while the basal portion forms the mons veneris cranially and the labia majora caudally. The median slit becomes the rima pudendi and the genital folds at its margins the labia minora.

In the male the phallic portion of the cloacal tubercle forms the greater part of the penis. The genital folds are not so fully developed in the male but the margins of the urethral groove bend medially over this depression and fuse along the median line converting it into the proximal urethra. The anterior extremity remains open as the external urethral orifice. The genital swellings disappear in the male, being replaced by an unpaired scrotal swelling.

Origin of the testis and ovary.—In their earlier stages no differences can be recognized between the ovary and testis. The undifferentiated sex-gland appears as a ridge on the medial side of the Wolffian body extending from the middle thoracic through the abdominal region. This ridge consists of a covering epithelium and an inner solid core formed by the ingrowth of this covering. Two types of cells may be recognized in the gland, those having their origin from the epithelium of the body cavity, and larger and less numerous germ-cells whose origin in man is uncertain.

Development of the testis and its ducts.—In the transformation of the indifferent genital gland into the testis the inner part of its epithelial core is converted into a network of solid cords, and the outer part forms a layer of dense mesenchyma which underlies the covering epithelium and represents the tunica albuginea testis. The network of solid cords is converted into the tubuli contorti (seminiferous tubules), the tubuli recti, and probably a portion of the rete testis.

With this differentiation of the genital gland the Wolffian body is also greatly modified. A number of the upper mesonephric tubules become connected with the rete testis and form the efferent ducts of the testis. The tubules above and below this group lose their connection with the Wolffian duct and remain as vestigial structures, certain of the upper ones forming the appendix testis and possibly the appendix epididymidis, and the lower ones the paradidymis. The Wolffian duct remains in its entirety as the ductus epididymidis, the ductus deferens, and the ejaculatory duct. The seminal vesicles arise as outgrowths of the ejaculatory duct. The Müllerian duct degenerates in the male, except for its lower extremity which remains as the prostatic utricle (the homolog of the vagina) and for its upper or cranial end which may give rise to the appendix epididymidis (fig. 1051).

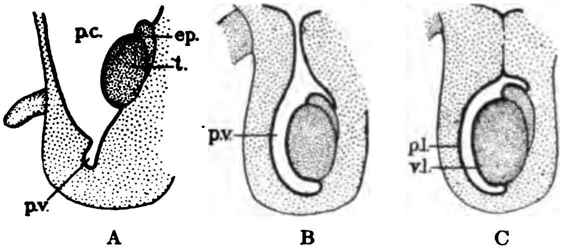
Development of the female genital tract.—In the female the core of the genital ridge forms the stroma of the ovary, the cells of the general covering epithelium give rise to the follicular cells, and the germ-cells which lie in the epithelium develop into the primitive ova (see fig. 1040).

The early changes in the Wolffian body resemble those of the male. The upper tubules degenerate with the exception of one or two which remain as the cystic *appendices vesiculosi* of the adult. The middle group of tubules form the *epoöphoron* (fig. 1042), a structure homologous with the efferent ducts of the testis but without function, which persists and increases in size until maturity. The lower group of tubules undergo a more complete involution although remnants of them persist in postnatal life as the *paroöphoron* (the homolog of the paradidymis). The Wolffian duct in the female loses its connection with the urogenital sinus but portions of it may be retained as the longitudinal duct of the epoöphoron or the duct of Gartner (homolog of the ductus deferens and ductus epididymidis).

The Müllerian duct is retained in its entirety in the female, the unpaired portion forming the uterovaginal canal and the paired portions the uterine tubes (fig. 1051). For the development of the broad ligament, see fig. 1040, p. 1297.

Descent of the testis and ovary.—In the latter part of the second fetal month the testes extend along the posterior wall of the trunk from the thoracic to the sacral region. In the third month they are found in the iliac fossæ, from the fourth to the seventh month at the level of the future internal abdominal ring, and in the eighth month they usually pass into the scrotum (fig. 60). The causes of the descent of the testes are obscure. Much of the early change in position is due not to the actual shifting of the organs but to the involution of their cranial parts. The later changes may be due in part to the contraction of the gubernaculum testis, an associated ligament of the fetal testis which contains smooth muscle.

FIG. 60.—DIAGRAMS OF THE DESCENT OF THE TESTIS. (From Lewis after Eberth.) ep., epididymis. p.c., peritoneal cavity. p.v. processus vaginalis. t., testis. p.l., parietal layer of the tunica vaginalis. v.l., visceral layer of the tunica vaginalis.



The passage of the testes through the inguinal canal is preceded by the invasion of the solid scrotum by a pocket of peritoneum, the saccus vaginalis, which later partially surrounds the testis as the tunica vaginalis. The connection between the saccus vaginalis and the abdominal peritoneal cavity is usually patent in the newborn, being commonly closed in the first 6 months after birth. For further details, see p. 1287.

The ovaries, like the testes, shift from an abdominal to a pelvic position in the early part of fetal life (fig. 49), although their final position is usually acquired in childhood. In their passage the axes of the ovaries are shifted first from the longitudinal to the transverse plane of the body and finally into the sagittal plane. The canal of Nuck, the homolog of the saccus vaginalis, is found in the labia majora in the female fetus. It is generally open at birth but is obliterated in early infancy.

The growth of the male genital organs.—The male organs of generation follow without exception the scheme of growth of the genital group of organs. They are characterized by rather rapid increase in the later fetal months and this phase may extend into the first months of postnatal life. Thereafter there is little change in their absolute weights until the prepuberal period, when a stage of rapid growth begins which may extend through adolescence into early maturity. Most of the male generative organs increase over thirty-fold in absolute weight n the postnatal period, being relatively heavier in the adult than in the newborn. However, he relative size of the testes is probably greater at the close of the embryonic period than at any subsequent time.

The growth of the female genital organs.—All of the female genital organs grow rapidly n fetal life and are relatively large at birth. In postnatal life the growth of the vagina, uterine tubes, and epoöphoron seem to follow the usual course of the genital organs. The postnatal growth of the ovaries is extremely irregular, the weight being influenced by the development of he ovarian follicles, a process which is active in childhood as well as in maturity. The uterus n the neonatal period undergoes a marked reduction in weight—a change which has been attributed to the withdrawal of a placental hormone at the time of birth. After this initial decrease there is little change in the size of the organ until the prepuberal period when it again enters on a phase of active growth. The adult dimensions are probably attained by puberty n the majority of cases. The paroöphoron does not increase in size after birth.

THE CELOMIC CAVITY

The general plan of the development of the celom as a cavity formed between the splanchnic and somatic layers of the lateral mesoderm has been outlined in connection with the development of the mesoderm (p. 12). In the higher mammals, including man, the celom first makes its appearance in the region of the heart as irregular clefts in the mesoderm on either side of the body. These spaces unite with one another by the formation of a communication which crosses the midline of the body below the heart. The common cavity formed by this fusion is known as the pericardial celom (fig. 61). The pleuroperitoneal portion of the celom is formed by the caudal extension of the celom in the lateral plates of the mesoderm on either side of the body. The peritoneal celom communicates freely with the extraembryonic celom at the margins of the embryonic disk.

FIG. 61.—DORSAL VIEW OF A RECONSTRUCTION OF AN EMBRYO ABOUT 2 MM. LONG, SHOWING THE EXTENT AND DIVISIONS OF THE EMBRYONIC CELOM. (After Dandy.)
Ht., heart. P.c., pericardium. P.C., parietal (pleural) canal. Pr., peritoneal cavity.

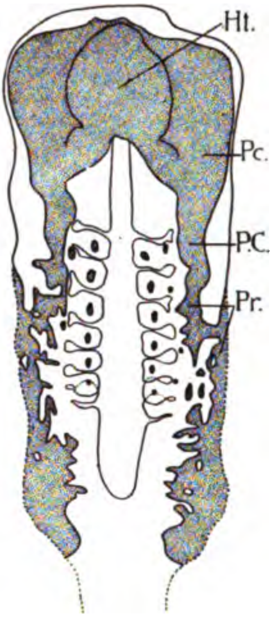
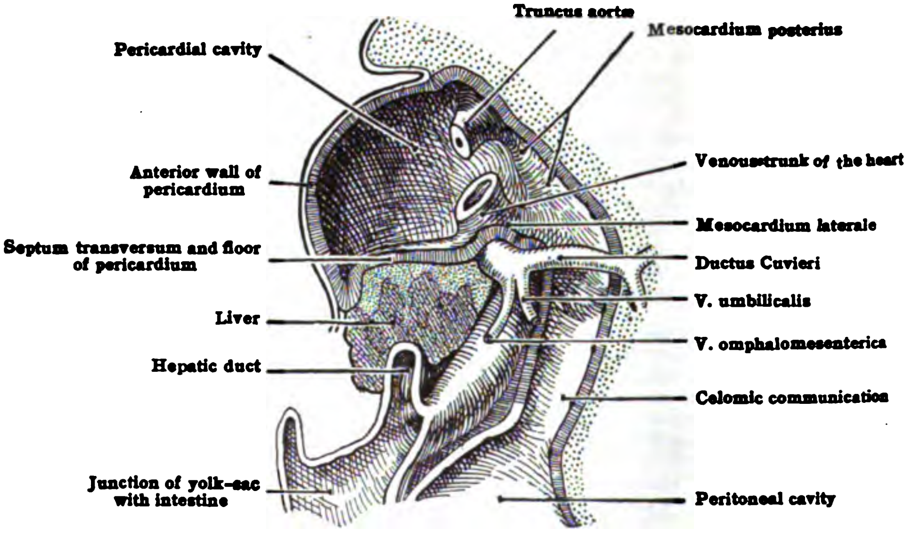


FIG. 62.—SAGITTAL SECTION SHOWING THE PRIMITIVE PERICARDIAL AND CELOMIC COMMUNICATION, SEPTUM TRANSVERSUM, LIVER, ETC., IN A HUMAN EMBRYO OF 3 MM. (After Kollmann, from a model by His.)

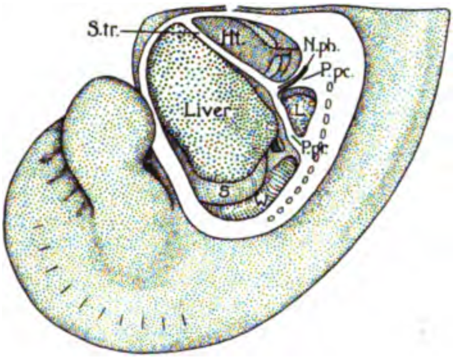


A single peritoneal cavity is formed from the two lateral ones as the embryo separates from the embryonic disk, and the ventral abdominal wall is formed. During this process the abdominal portion of the archenteron is enclosed between the right and left layers of splanchnic mesoderm which are reflected upon it from the dorsal and ventral abdominal walls. These layers remain dorsal to the archenteron as the dorsal mesentery. They also remain ventral to the archenteron from the end of the cavity to the umbilical region as the ventral mesentery. Caudal to the umbilicus, however, the ventral mesentery disappears and the right and left peritoneal cavities become confluent. The formation of the ventral body-walls also separates the peritoneal cavity from the extraembryonic celom, although an extraembryonic extension of the peritoneal cavity, the *umbilical celom*, remains in the root of the umbilical cord through the embryonic period.

The separation of the peritoneal, pericardial and pleural cavities.—The final divisions of the celom are separated by the formation of the diaphragm and the lateral walls of the middle mediastinum. As will be seen from figs. 61 and 62, the pericardial celom communicates with the peritoneal portion of the celom only by a pair of lateral passages, the *parietal canals*. These channels are separated in the midline by the anterior part of the yolk-stalk and by the vitelline-umbilical trunks which pass along this structure to reach the heart. The media partition formed by these structures with their covering of splanchnic mesoderm is called the septum transversum and is the fundament of the greater part of the diaphragm. In the later shifting of the septum transversum the cranial parts of the parietal canals become funnel-shaped spaces which are invaded by the lung-buds and which form the fundaments of the *pleural cavities*. The pleural cavities become separated from the pericardial cavity by the *pleuropericardial membranes* which arise from the dorsal and lateral walls of the parietal cavity enclosing the phrenic nerve. The caudal openings of the pleural cavities into the peritoneal cavity become closed by the *pleuroperitoneal membranes* which arise from the dorsal margin of the septum transversum and extend dorsolaterally to unite with the dorsal abdominal wall (fig. 63).

Fig. 63.—Lateral View of an Embryo 11 mm. Long, Showing the Pleuroperitoneal (P. pr.) and the Pleuropericardial Membranes. (P. pc.). (After Mall.)

Ht., heart. L., lung. N.ph., phrenic nerve. S., stomach. S.tr., septum transversum. W, Wolffian body.



The fundament of the diaphragm is formed in the upper cervical region and rapidly shifts caudally in the embryonic period. The musculature of the diaphragm is derived from premuscle masses which are formed in the cervical region.

The further history of the peritoneum is considered with its adult anatomy (p. 1172). The development of the tunica vaginalis is outlined in connection with the descent of the testes (p. 53). For relations to hernia, see p. 1397.

THE DUCTLESS GLANDS

The several varieties of ductless glands have little in common in their germ-layer origin, in the method of their early development, or in the course of their subsequent growth.

The thyroid gland.—The thyroid gland appears in embryos of the third week as a shallow median depression of the floor of the pharynx at the level of the first and second branchial pouches (fig. 37*A*). This outgrowth is converted into a solid mass which for a variable period remains connected with the pharynx by a solid stalk, but which eventually becomes detached and migrates into the region of the neck occupied by the definitive thyroid gland (cf. p. 1316). The solid mass is broken into a number of fenestrated epithelial plates from which the thyroid follicles are developed. Colloid appears in the thyroid follicles about the third fetal month. The disappearance of the colloid at birth and also the desquamation and partial destruction of the follicular epithelium have been described, but are of doubtful significance.

The thyroid assumes its bilobed form at an early stage (fig. 41). Its stalk may persist in part as the pyramidal lobe of the gland and portions of it occasionally remain as isolated thyroid masses in the upper cervical region or in the base of the tongue. The foramen cecum of the tongue presumably marks the point of its pharyngeal attachment.

At birth the thyroid weighs from 2 to 3 grams and its weight increases 10 to 15-fold in postnatal life. The postnatal changes in weight follow the course of the visceral group of organs.

The parathyoid glands.—The parenchyma of the parathyroid glands is formed from the thickened lateral walls of the dorsal extremities of the third and fourth pharyngeal pouches (fig. 41, Ep. III and Ep. IV). These masses become detached from the pouches in the second month and then migrate to their adult position. For further details, see p. 41.

The pineal body.—The pineal body (epiphysis cerebri) arises in the fifth week as a diverticulum from the caudal extremity of the roof of the diencephalon (fig. 641). The distal portion of this pouch becomes the body of the epiphysis. The proximal portion remains as the stalk. Ingrowths of connective tissue from the pia mater later divide the body of the organ into lobules. At birth the structure is relatively large and by 12 years it has obtained its full size. Structural involution of the pineal body begins about the sixth or seventh year and is practically complete by puberty.

The hypophysis cerebri.—The anterior or glandular lobe of the hypophysis cerebri (pituitary body) is formed from the extremity of Rathke's pouch from the oral sinus, while the posterior or neural lobe is formed from a part of the infundibular depression in the floor of the forebrain. These two structures come in contact in the fourth week. The extremity of Rathke's pouch soon becomes detached and partially incloses the neural portion. In the second month the walls of Rathke's pouch are differentiated into cords and tubules which form the trabeculæ and acini of the hypophyseal parenchyma and obliterate the greater part of its central cavity. The infundibular portion undergoes less extensive changes. The greater part of the stalk of Rathke's pouch usually disappears but a portion of its lower part probably forms the *pharyngeal hypophysis*, a constant glandular mass resembling the anterior lobe of the hypophysis and located in the region of the pharyngeal tonsil (see fig. 1069).

The hypophysis weighs about 0.12 grams in the newborn and its mass increases 5 or 6 times between birth and maturity. The curve of the postnatal increase in the absolute weight of the hypophysis is shown in fig. 24. It is characterized by a rapid rise in infancy and early childhood and a slow but steady growth thereafter to maturity.

The thymus.—While a part of the thymus is of branchial origin and the organ is commonly classed with the ductless glands, both its finer structure and the course of its growth indicate a close relationship with the lymphoid organs. In man the thymus first appears as outgrowths of the walls of the third and (inconstantly) of the fourth pair of branchial pouches (fig. 41). Usually the lower portion of the third pouch is converted into a long epithelial tube the lumen of which is soon obliterated. Its walls are reduced to a reticular network whose meshes are invaded by numerous lymphocytes. The thymic (Hassal's) corpuscles are formed by the secondary aggregation of reticular cells of entodermal origin. For further details, see p. 1321.

In its growth the thymus follows the typical course of a lymphoid organ (fig. 24). At birth it forms about 0.42 per cent. of the body. This relative weight drops to 0.12 per cent. in later childhood, 0.09 per cent. in adolescence and 0.05 to 0.02 per cent. in early maturity. The absolute weight rises from about 13 grams at birth to about 38 grams at puberty and then declines. The weight of the thymus is at all periods subject to great individual variation. After birth the parenchyma forms a constantly decreasing proportion of the thymus.

In the fetus the thymus occupies the anterior part of the superior mediastinum and often a little of the lower cervical region. Its thoracic portion is usually widely expanded coming in contact with the anterior chest wall over a considerable area. With the establishment of respiration at birth the gland is pressed between the expanding medial borders of the lungs and moulded into the more elongate form which is characteristic of infancy and childhood (figs. 1058, 1059).

The chromaffin bodies.—The cells of the various masses of chromaffin tissue (aortic bodies, carotid bodies, cardiac bodies, etc.) have their primary origin in the neural crest (see p. 1321) and form a part of the stream of cells which migrate to the ventral side of the vertebral column. These walls give rise both to cells of the sympathetic ganglia and to the chromaffin cells, the distinction between the two becoming evident in the latter part of the second month. The chromaffin bodies form prominent structures in the fetus and newborn, the largest being the aortic bodies which are located on either side of the abdominal aorta (fig. 1066). After infancy they undergo partial involution.

The suprarenal glands.—The suprarenal glands have a dual origin, the medulla being formed of chromaffin tissue (vide supra) and the cortex from the lining of the celom. The cortex appears in the fourth week as buds of celomic epithelium which project from the root of the mesentery into the loose mesenchyma. These form a compact isolated mass of epithelial cords lying on either side of the aorta. The medulla is formed by the migration of chromaffin cells into the center of the mass of cortex. This process begins in the second month and continues through the greater part of the fetal period. For further details, see p. 1324.

The suprarenals follow a peculiar growth-cycle (fig. 24). Growing rapidly in fetal life they acquire an average weight of about 7 grams at birth. During the period of the newborn they undergo a rapid decrease to about one-third of their natal weight. There is little increase in weight in infancy or early childhood but apparently a rapid phase of growth in middle or later childhood and a slower gain thereafter. The relative weight of the suprarenals is approximately 0.46 per cent. of the body-weight from the fourth fetal month until birth. Following the postnatal decrease it drops to about 0.15 per cent., rising again to about 0.2 per cent. in the adult. The neonatal decrease of the suprarenals is caused by the involution of the middle and inner cortical zones, which are not regenerated from the outer zone until after the middle of the first period of childhood.

THE SKIN AND APPENDAGES

The skin.—The epidermal portion of the skin is formed from the surface ectoderm of the embryo while the dermis is derived from the underlying mesenchyma. In an early stage the epidermis consists of two layers, a surface layer of flattened cells, the periderm, and a basal layer of columnar germinative cells. The layers of the epidermis recognizable in the adult skin do not appear until about the middle of the of fetal life. The dermis becomes distinguishable from the underlying tela subcutanea in the third month but its division into reticular and papillary layers does not occur until late in fetal life. The hair-follicles are formed from solid downgrowths of the germinal layer of the epidermis. The first appear at the close of the second month but the general hair-coat does not form before the fourth month. New hair-follicles are formed until birth and probably for some time thereafter. The first hairs or fetal lanugo are soon shed, the process beginning before birth, and a second shedding of the infantile hair, including the hair of the eyelashes and crown, takes place about the end of the first year. After this time there is a constant hair-change but no definite periods of shedding can be recognized. The sebaceous glands arise as lateral outgrowths of the developing hair-follicles. The sudoriferous glands (sweat glands) are formed as solid downgrowth of the epithelium in the fourth or fifth months. All of the sudoriferous glands are formed in fetal life. For further details on the development of the skin, see pp. 66, 69.

The areas occupied by the nails are marked out on the dorsal surface of the digits in the early part of the third month. The epithelium at the proximal margin of the nail-area is invaginated forming the proximal or posterior nail-fold which projects into dermal mesenchyma, and smaller folds are formed at the lateral margins of the nails. The middle cells of the invagination form the horny layer of the nail and the lower cells form the germinative layer. The upper cells or periderm form a superficial covering, the *eponychium*, which is later thrown off except for a narrow proximal margin which persists through life. The dermal mesenchyma underlying the epithelial nail forms the nail-bed. For the growth of the nails, see p. 70.

The mammary glands.—In the fourth week a thickening of the surface ectoderm, the mammary line, is formed on either side of the trunk extending from the anterior to the posterior limb-bud. The portion of the mammary line in the region of the future mammary gland forms a solid mass of epithelium, the mammary hillock. The lactiferous ducts develop as outgrowths from the basal portion of the mammary hillock and the minor ducts and alveoli of the gland are formed through the further growth and subdivision of the lactiferous ducts. For further details, see p. 79.

Soon after birth a slight secretion (witch's milk) is formed in the lactiferous ducts of the mammary glands of both male and female infants. Ordinarily this secretion ceases by the close of the third postnatal week. There is little change in the structure of the mammary gland in childhood but in the latter part of the prepubertal period in the female there is a rapid growth of the gland parenchyma together with an increase in the adipose and elastic tissue.

References on developmental anatomy.—*Embryology*: Keibel and Mall, Human Embryology (2 vols.); McMurrich, Development of the Human Body; Bryce, Quain's Anatomy, 11th ed., vol 1; Keith, Human Embryology and Morphology; Broman, Normale und abnorme Entwicklung des Menschen. *Growth*: Minot, Age, Growth and Death; Jackson, Amer. Jour. Anat., vol. 9; Anat. Record, vol. 3.; Retzius, Biol. Untersuch., vol. 11; Dufestel La Croissance. *Postnatal Development*: Bardeen, Carnegie Contributions to Embryology, No. 49: Ballantyne, Introduction to the Diseases of Infancy; Symington, The Topographical Anatomy of the Child; Scammon, Outline of the Anatomy of the Infant and Child, Abt's System of Pediatrics, vol. 1.

SECTION II

THE SKIN AND MAMMARY GLANDS

LARGELY REWRITTEN FOR THE SIXTH EDITION

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THE SKIN

THE bodies of all animals present a modified surface layer inclosing and protecting their more delicate inner parts. The existence of the individual largely depends upon the integrity of this limiting envelope and through it exchanges between the environment and the individual must take place. In the lowest animals such a modified surface layer is known as the ectoplasm, perisarc, theca, coat, etc. while in man and higher animals it is the skin. When an area of skin is destroyed the fluids of the body flow out freely and the elements of the environment invade the exposed parts. If the destruction of skin be too extensive, the individual is unable to maintain itself and actually disintegrates into the environment. On the basis of such a conception, the skin becomes one of the most important and complicated organs of the body, both as to structure and functions.

The human skin, or **common integument** [integumentum commune], covering the entire surface of the body and blending with the epithelial lining of the inner tubes at their orifices is so constructed as to maintain wide physical and chemical differences between the internal structures on the one side and the external environment on the other. At the same time the skin permits exchanges of fluids and, through special modifications, supplies all sensory communication and appreciation of the surrounding world.

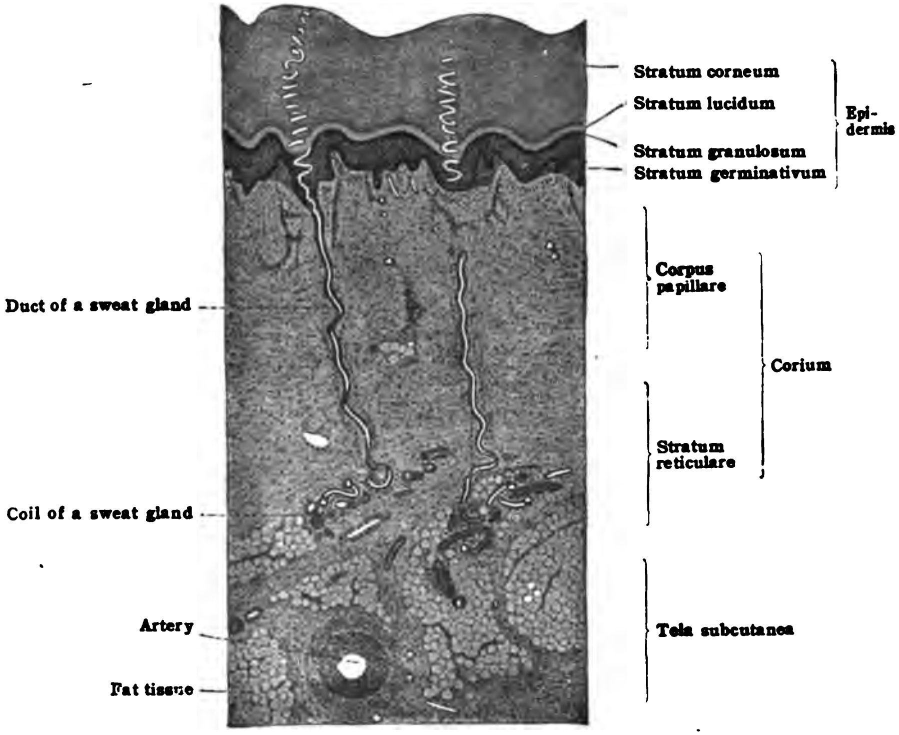
The *primary function of the skin* is protective, but in addition and in connection with this function it supplies the mechanism for regulating or maintaining the body-temperature, the sensory apparatus for receiving impressions, widely distributed glands for the secretion of sweat and sebum, local glands secreting waxes and the milk-glands on which the existence of the race has depended. The skin also possesses slight powers of excretion, respiration and absorption. Its outer layer further gives rise to the hair and nails which are protective in nature.

The receptor portions of the organs of special sense are developmental modifications of the embryonic skin. Thus all means of acquaintance with the world about must depend primarily upon skin-organs. And finally the stimuli received by the organs of special sense are conveyed to the central nervous system, the brain and spinal cord, which in evolution and embryonic development represent a modified portion of the embryonic skin or ectoderm. The skin of animals, broadly speaking, is the protective and sensory sheath enclosing the body.

Layers.—The skin consists of two principal layers. The outer layer, **epidermis** or scarf-skin, contains no vessels and is derived from the ectoderm. This is truly the protecting layer and from modifications of it the hair, nails and skin-glands as protective organs are derived, although these may later extend deep into the underlying tissues (fig. 64). Immediately below this outer epithelial epidermis lies the **corium** (cutis, derma) or connective tissue skin. This is richly supplied with blood and lymph-vessels and from these the epidermis is nourished. Sensory end-organs and nerves are also very abundant in the corium. Further details of structure of the corium and its relation to the surface patterns of the epidermis are described later. The corium passes imperceptibly into a deeper, looser connective tissue layer, the **tela subcutanea** or superficial fascia, which serves to connect more or less loosely the corium or skin proper to the deep fascia or underlying tissues.

Thickness.—In general the skin on the more exposed or extensor surfaces of the body and extremities is thicker and less sensitive than on the ventral surfaces yet on the palms and soles it is thicker than in any dorsal region except the neck and interscapular back region. At the same time the palm and sole skin is highly sensitive. The average thickness is from 1 to 2 mm.; but over the tympanic membrane and eyelids it may be less than 0.5 mm., while on the back it may reach almost 5 mm. in thickness.

FIG. 64.—VERTICAL SECTION OF THE SOLE OF THE FOOT OF AN ADULT. ×25. (Lewis and Stöhr.)



The **color** of the dorsal skin and also of the dorsal hair, which includes the head-hair, is darker than the ventral skin and ventral hair, such as the beard. An individual may have black crown hair and a lighter or red beard but rarely, if ever, the reverse arrangement.

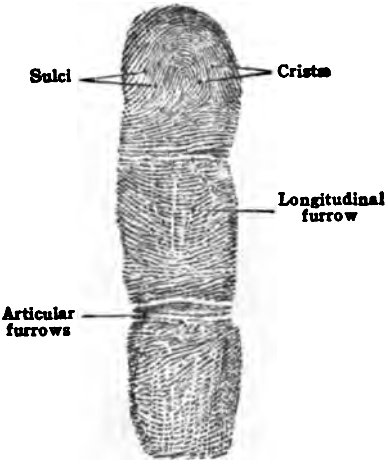
The color of the skin has considerable general significance and the races of mankind are roughly separated on such a basis into Caucasian or white, Mongolian or yellow, Malay or brown, Indian or red, Ethiopian or black. The hair and eye-color are very dark brown or black in all races except the white. This race of mankind alone shows golden or flaxen hair and blue eyes. The color of the skin varies with the amount of melanin pigment present in the deepest layers of the epidermis, being black in the negro where it is most abundant and decreasing in the different races to the scantest amount in the blonde Caucasian. The blood in the cutaneous vessels also affects the color of the skin, giving the pinkish complexion to the albino and blonde; in the brunette often producing a dark color below the eyes and about the lips. The influence of the blood on skin-color is readily appreciated by noting the blueness of the lips and fingers when very cold, the scarlet flush of anger, and the pallidness of fear.

The skin of blondes on exposure to strong sunlight or cutting winds becomes red, and usually shows later irregular pigmented spots or *freckles*. Darker individuals become uniformly pigmented or *tanned* on exposure. Both tan and freckles are more or less transient and generally disappear when the body is no longer exposed.

Complete absence of pigment from the skin gives the condition known as albinism. Partial absence of pigment or white spots at times occur; if congenital the condition is known as leukoderma, if acquired it is called vitiligo.

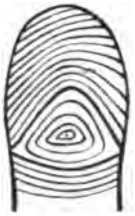
Young children of darker races, e. g., Japanese and Chinese, occasionally present a bluish pigmentation known as 'blue Mongolian spots' of the skin over the sacral, coccygeal and ischial regions. This also occurs rarely in white children. The appearance is due to the presence in the corium of spindle-shaped or stellate pigment cells, chromatophores, resembling the pigment cells of the choroid layer of the eyeball. Similar cells are found distributed generally in the corium of monkeys' skin and their occurrence in man has been thought to be of possible phylogenetic significance.

FIG. 65.—FINGER PRINT (NATURAL SIZE) SHOWING CRISTÆ AND SULCI.



The **elasticity and strength** of the skin are due to the corium, and this layer when tanned or cured gives leather. The skin is more elastic or stretchable over certain regions than others and this property varies in different individuals. The skin is more lightly attached to underlying parts in certain regions, and is here very movable. Its elasticity is well shown under these conditions. If an arm be firmly grasped with the hand it will be found that the skin may move up and down over the underlying muscles as if it were a sleeve. The degree of motility of the skin is appreciated in surgical operations.

FIG. 66.—DIAGRAM SHOWING THE ARRANGEMENT OF THE PRINCIPAL CRISTÆ OF THE THUMB.

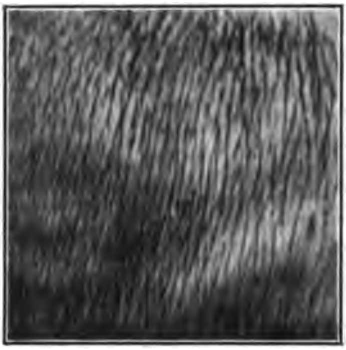


The infinite folds and irregularities on the surface of the skin along with its loose under attachment and elastic nature render it *distensible* to a considerable extent. Roughly speaking, the skin of an individual is sufficiently extensive to cover a body of much larger size. Under certain conditions a leg, for example, may swell to double the usual size but the skin stretches to cover it. The skin over such a swollen part is smoother and more glistening than usual, since the minute folds and patterns are obliterated or smoothed out by the expansion. When increase in size is gradual such as normally occurs during pregnancy the skin area may be stretched to four or five times its previous extent. In these cases the skin is often injured and short parallel, slightly reddish streaks occur which after reduction in size become the silvery white lines, or striæ seen in the abdominal skin of a woman who has borne children.

The **surface-area** of the skin corresponds approximately to the surface of the body and naturally varies with the size of the individual. It has been variously estimated at from 10,500 to 18,700 sq. cm. for a medium-sized adult male. For the area in children, see p. 23.

Folds and furrows.—The skin presents elevations and depressions due to the fact that it follows more or less closely the contour of the underlying structures, but in addition to this it possesses certain elevations and depressions peculiarly its own. They are found on the skin in various parts of the body. Some are permanent, others only temporary. Large permanent **folds** which include all the layers of the skin are seen, as the prepuce of the penis and the pudendal labia. The most marked depression is the **umbilical fovea.** Other conspicuous folds and furrows are seen in the neighborhood of the lips and eyelids. Certain other less permanent folds and furrows are produced by the action of the joints, **joint-furrows,** and of the muscles of expression of the skin, **'wrinkles.'**

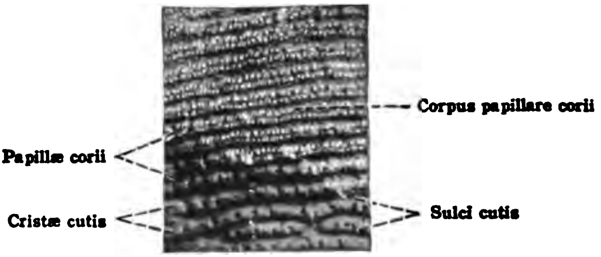
Fig. 67.—From a Photograph of the Superficial Furrows on the Back of the Hand. (× 1.)



Other minute folds and furrows which affect only the epidermis and the superficial layer of the corium are seen in various places. These are represented by the numerous fine superficial creases, unassociated with elevations, forming rhomboidal and triangular figures over almost the whole of the surface of the skin (figs. 65, 66). They are especially numerous on the dorsal surface of the hands (fig. 67). The fine curvilinear ridges [cristæ cutis] with intervening furrows [sulci cutis] arranged in parallel lines in groups on the flexor surface of the hands and feet are also of this type. They form patterns characteristic for each individual and permanent throughout life.

Among the projections are the large permanent folds of skin such as the **labia pudendi,** the **preputium penis,** the **frenula preputii, clitoridis,** and **labiorum pudendi,** and less marked ridges as the median **raphe** of the perineum, scrotum and penis, and the **tuberculum labii superioris.** Of a somewhat different sort are the **touch pads** [toruli tactiles] of the hands and feet. Among the larger depressions in addition to the **umbilical fovea,** is the **coccygeal foveola,** and a considerable number of well-marked permanent furrows found in various places, such as the **nasolabial** and **mentolabial sulci,** the **philtrum labii superioris,** the **infraorbital sulcus,** and the **infra- and supraorbital palpebral sulci.** There are numerous **articular furrows** on both the flexor and extensor surfaces produced by the action of the joints, and associated with intervening folds of skin, particularly on the dorsal surface. They are especially noticeable on the hands. Variations of the palmar joint-sulci are due to variations in opposition of the thumb and the use of the fingers and the relative arrangement of the thumb and fingers and joints. They are of importance as indicating topographically the position of the joints, their relation to which has been made clearer by means of the X-ray.

Fig. 68.—From a Photograph of the Skin Ridges and Papillæ of the Palm of the Hand. Epithelium Completely Removed Above; Partly Removed Below. (× 5.)

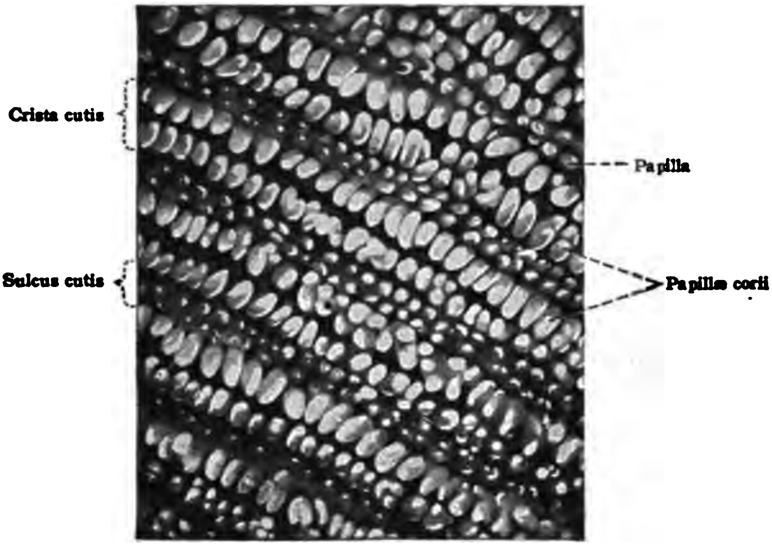


The folds and furrows brought about through the action of the skin muscles run at right angles to the muscle fibers and are more or less transitory at first but become more permanent through repeated or long-continued action. They are represented by the **wrinkles** of the forehead, the lines of expression of the face, the transverse wrinkles of the **scrotum** and the **radiating** folds around the anus. The more superficial **cristæ cutis** and **sulci cutis** are arranged in groups within and around the touch pads, on the volar surface of the hands and the plantar surface of the feet (figs. 65, 66). The cristæ of each group are parallel. They correspond to the rows of papillæ of the corium. Since the patterns of the cristæ and sulci are characteristic for the individual, and permanent from youth to old age, they have been classified in a number of types and are important as a means of identification.

There are also a great number of minute depressions which mark the points where the hairs pierce the surface and where the glands open. These are popularly known as **pores.** Under the influence of cold and emotion the hair muscles contract and cause a slight elevation of the skin at the point where the hair emerges. This roughened appearance of the skin is generally known as 'goose-flesh.'

A complex wrinkling of the skin appears in old age, or in the course of exhausting diseases, as a result of loss of elasticity and from absorption of the cutaneous and subcutaneous fat. Rounded depressions called **dimples** are produced by the attachment of muscle-fibers to the deep surface of the skin, as on the chin and cheek, and are made more evident by the contraction of these fibers. Others are produced by the attachment of the skin by fibrous bands to bony eminences, as the elbow, shoulder, vertebræ, and posterior iliac spines. They are best. seen when the subcutaneous adipose tissue is well developed.

Fig. 69.—Papillæ of the Corium after Maceration. From Retouched Photograph Epithelium Removed by Maceration. (× 25.)



Structure of the corium.—The superficial layer of the corium is of fine, close texture, free from fat, and forms a multitude of eminences called **papillæ corii** (figs. 68, 69) which project into corresponding depressions on the deep surface of the epidermis. For this reason this part of the corium although but indistinctly separated from the deeper layer is called the **corpus papillare.**

Some of the papillæ contain vessels, other nerves, hence they are known as vascular or tactile papillæ. They are very closely set, varying considerably in number in different parts of the body from 36 to 136 to a square millimeter and it has been estimated that there are about 150 million papillæ on the whole surface.

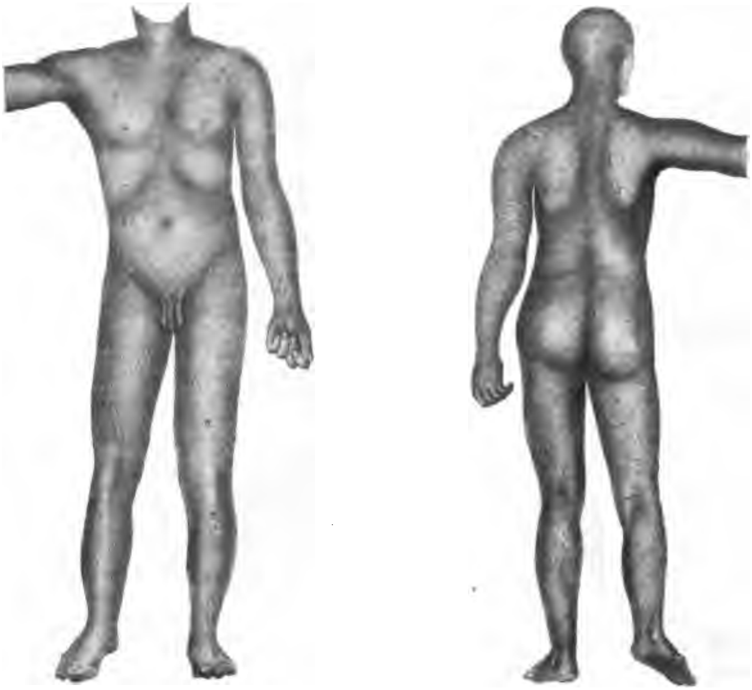
The deeper layer of the corium, the **tunica propria** (stratum reticulare), is composed of coarse loose bands of fibrous tissue intermingled with small fat lobules. The fibrous and elastic tissue is arranged for the most part in intercrossing bundles nearly parallel to the surface of the skin.

The bundles running in some directions are usually more strongly developed and more numerous than those in others, but the direction of the strongly developed bundles varies in different parts of the body. In general those are best developed which have a direction parallel with the usual lines of tension of the skin, hence it results that wounds of the skin tend to gape most at right angles to these lines. The bundles take a direction nearly at right angles to the long axis of the limbs, and on the trunk run obliquely, caudally, and laterally from the spine (figs. 70, 71). On the scalp, forehead, chin, and epigastrium, equally strong bundles cross in all directions, and a round wound, instead of being linear as elsewhere, appears as a ragged or triangular hole. The arrangement of the connective tissue bundles influences the arrangement of the blood-vessels of the skin.

The quantity of *subcutaneous fat* varies considerably in different parts of the body. It is, for instance, entirely absent in the penis, scrotum, and eyelids. When it is abundant, the subcutaneous layer is known as the *panniculus adiposus.*

In some situations, as in the caudal portion of the abdomen and in the perineum, the connective tissue is so arranged that the panniculus may be divided into layers, so that a superficial and a deep layer of the superficial fascia may be recognized. The fat is well developed over the nates, volar surface of the hands and plantar surface of the feet, where it serves as pads or cushions; in the scalp it appears as a single uniform lobulated layer between the corium and the aponeurosis of the epicranial muscle; and on other parts of the surface it is somewhat unequally distributed and shows a tendency to accumulate in apparent disproportion in some localities, as on the abdomen, over the symphysis pubis, about the mammæ in females, etc. Everywhere except on the scalp it may undergo rapid and visible increase or decrease under the influence of change of nutrition.

Figs. 70 and 71.—Diagrams Showing the Arrangement of the Connective Tissue Bundles of the Skin on the Anterior and Posterior Surfaces of the Body. (After Langer.)



Skin-muscles.—In the subcutaneous tela and the corium muscle fibers are found in larger or smaller groups. These are of two kinds, striated and unstriated (smooth) fibers.

Subcutaneous planes of *striated muscle* are relatively scanty in man when compared with the great panniculus carnosus of the lower mammalia. This is mainly represented by the platysma in the neck which has both its origin and part of its insertion in the skin. Closely associated with this are the muscles of expression of the face and the palmaris brevis muscle which have one end terminating in the deep surface of the skin. The epicranial muscle is also considered by some to belong to this group.

Smooth muscle fibers are scattered through the corium collected into bundles in the neighborhood of the sebaceous glands and the hairs. They are described in connection with these latter (p. 68). In addition to these muscles are found in the scrotum as the dartos, in the perineum, around the anus, and beneath the papilla and areola of the mammary gland.

Bursæ mucosæ subcutaneæ.—In some situations where the integument is exposed to repeated friction over subjacent bones or other hard structures its movements are facilitated by the development of sac-like interspaces in the subcutaneous tissue, the **subcutaneous mucous bursæ.** They are similar to the more deeply placed bursæ which are found in relation with muscle tendons. Their occurrence is quite variable. In some individuals they are numerous, in others very few. They have a considerable practical importance from the fact that they may become greatly swollen.

OBSERVATIONS ON THE CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF POSTNATAL LIFE

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In the transition from intrauterine to extrauterine life few organs of the body are more affected than the stomach. The change influences many characters of the organ's morphology, and the position, the mass, the finer structure, and particularly the capacity are rapidly modified and adjusted to the new conditions and functions of postnatal life.

The changes in gastric capacity in this period of transition have not been studied very intensively. As early as 1856 Guillot[1] published some data regarding physiologic gastric capacity in the first few days of extrauterine life and this was followed somewhat later by a more extensive study by Bouchaud.[2] Since that time further information on the subject has been published by Hillebrand,[3] Kruger,[4] Ssnitkin,[5] Cammerer,[6] Tuley,[7] Jaschke,[8] Landois[9] and others. The figures presented in most of these studies are not extensive, and are usually incidental to more general studies of metabolism in the neonatal period. Much of the early work is no longer of more than historic value because the observations were made under conditions

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1. Guillot, N.: De la nourrice et du nourrisson, Union méd., 1852, p. 61.
2. Bouchaud: De la mort par inanition et études experimentales sur la nutrition chez le nouveau-né, Thèse, Paris, 1864.
3. Hillebrand, F.: Untersuchungen über Milchzufuhr und über die Jodkaliumausscheidung des Saüglings, Arch. f. Gynäk. **15**:453, 1885.
4. Krüger, G.: Ueber die zur Nährung Neugeborener erforderlichen Milchmengen mit Rücksicht auf die Gewichtsveränderungen der Kinder, Arch. f. Gynäk. **7**:59, 1875.
5. Ssnitkin, N.: (The Quantity of Breast-Milk Consumed by Sucklings), Allg. med. Centr. Ztg. **45**:317, 1876.
6. Cammerer, W.: Der Stoffwechsel eines Kindes im ersten Lebensjahr, Ztschr. f. Biol. **14**:383, 1878.
7. Tuley, H. E.: Observations on the Capacity of the Stomachs of Infants Under Ten Days of Age, Arch. Pediat. **10**:423, 1893.
8. Jaschke, R. T.: Neue Erfährungen in der Technik der Ernährung sowie zur Physiologie und Pflege des Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **35**:60, 1912.
9. Landois, F.: Zur Physiologie des Neugeborenen, Monatschr. f. Geburtsh. u. Gynäk. **22**:194, 1905.

which no longer obtain in modern infant feeding. Regarding anatomic capacity in this period, we have still less accurate information, the only extensive series of measurements being that of Alliot[10] on newborn children.

It has been pointed out recently that, during the greater part of the suckling period, there exists a fairly definite and constant relation between the anatomic capacity of the stomach, as determined postmortem, and the physiologic capacity as ascertained by weighing the child before and after feeding.[11] And it has been found that the capacity of the stomach increases at a very definite rate in early life despite the numerous fluctuations due to differences in physical constitution and to varying physiologic factors. It is the purpose of the present paper to trace the changes which these measures of gastric capacity undergo in the neonatal period, to ascertain the main factors which influence them, and to determine, in as far as possible, how soon after birth the relations and the rate of growth in capacity which are characteristic of the suckling period are established.

Through the kindness of Dr. J. P. Sedgwick, chief of the department of pediatrics, we have had access to the records of the Pediatric Section of the Elliot Memorial Hospital of the University of Minnesota. From these we have taken the records of the amount of individual feedings, as determined by weighing before and after nursing, of 323 children during the first ten days of life. In all we secured 14,571 individual records of physiologic gastric capacity as determined by this method. The distribution of these records according to days and to the birth weights of the individuals observed is shown in Table 1. To avoid confusion we have not included a statement of the number of cases in later tables but this record can be ascertained in all cases by reference to Table 1.

Our study was limited to children having a birth weight of 2,000 gm. or over, and no twins were included in the group. Otherwise the cases were taken seriatim from the hospital records. In this group there were 187 males and 136 females. The average weight at birth of the males was 3,349 gm. and of the females 3,254 gm. These figures are somewhat below the averages determined by Taylor[12] in his study of the new-born of this same clinic, but this discrepancy is probably due to the fact that Taylor, desiring to establish a norm for full term children, excluded, as far as possible, all prematures.

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[10] Alliot, L.: La capacité stomicale du nouveau-nè, Thèse, Paris, 1905.

[11] Scammon, R. E.: Some Graphs and Tables Illustrating the Growth of the Human Stomach, Am. J. Dis. Child. **17**:395 (May) 1919.

[12] Taylor, R.: The Measurements of 250 Full-Term, New-Born Children, Am. J. Dis. Child. **17**:353 (April) 1919.

The average weight of the new-born in this same clinic as determined by Ramsey and Ally,[13] studying 300 cases, was 3,391 gm. for males and 3,276 gm. for females.

The children were breast fed five times per day, but many babies did not secure their full quota of feedings on the first day as is indicated by the small totals both of cases and feedings in column 2 of Table 1. After the first day the number of missed feedings was negligible.

TABLE 1.—Material Used in the Study of Physiologic Gastric Capacity *

Age in Days	Number of Cases and Number of Feedings					
	Group I 2,000 to 2,500 Gm. Birth-Weight (Aver. 2,260 Gm.)	Group II 2,500 to 3,000 Gm. Birth-Weight (Aver. 2,840 Gm.)	Group III 3,000 to 3,500 Gm. Birth-Weight (Aver. 3,246 Gm.)	Group IV 3,500 to 4,000 Gm. Birth-Weight (Aver. 3,731 Gm.)	Group V 4,000 Gm. and Above Birth-Weight (Aver. 4,143 Gm.)	All Cases (Aver. 3,315 Gm.)
1	5 (10)	32 (74)	71 (154)	31 (63)	14 (63)	153 (364)
2	14 (65)	63 (311)	143 (698)	75 (370)	28 (135)	323 (1,579)
3	14 (70)	63 (308)	143 (713)	75 (371)	28 (136)	323 (1,598)
4	14 (70)	63 (313)	143 (713)	75 (374)	28 (139)	323 (1,609)
5	14 (69)	63 (315)	143 (712)	75 (373)	28 (138)	323 (1,607)
6	14 (70)	63 (314)	143 (714)	75 (373)	28 (138)	323 (1,609)
7	14 (70)	63 (313)	143 (714)	75 (373)	28 (138)	323 (1,608)
8	14 (70)	63 (315)	142 (710)	74 (370)	28 (140)	321 (1,605)
9	14 (70)	63 (314)	141 (700)	74 (368)	28 (138)	320 (1,590)
10	14 (62)	59 (279)	135 (614)	71 (331)	28 (116)	307 (1,402)
Total No. Feedings	(626)	(2,856)	(6,442)	(3,366)	(1,281)	(14,571)

* The upper figures represent the number of cases; the lower figures, in parentheses, indicate the number of feedings.

From these data was determined the average physiologic capacity, the average maximum physiologic capacity, the average capacity in per cent. of the body weight at birth, the average maximum capacity in per cent. of the body weight at birth, the average and average maximum capacity in first born and later children, the excess of the average maximum capacity over the average capacity, and the percentage increment of the average capacity and the average maximum capacity. These determinations were made for each day of the period under consideration, first for the entire series of cases and later for the same cases grouped into five classes according to birth weight.

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[13] Ramsey, W. R., and Alley, A. G.: Observations on the Nutrition and Growth of New-Born Infants. Am. J. Dis. Child. **15**:408 (June) 1918.

The average deviation and the average percentage deviation was determined for the average capacity in the group of cases having a birth weight ranging from 3,000 to 3,500 gm. The average and average maximum capacity in males and in females was also determined in this group.

Average physiologic capacity.—The average physiologic capacity, for all children having a birth weight of 2,000 gm. or over is shown in the seventh column of Table 2 and the curve labeled "B" in Figure 1 illustrates it graphically. The average physiologic capacity of such children as received feedings on the first day was 7 gm. This was almost doubled on the second day (13 gm.) and almost quadrupled on the third day (27 gm). On the fourth day the average capacity was a little more than six times that of the first day (46 gm.). After the fourth day the increase in average capacity was much less rapid, although it was still continued, and on the tenth day it was 81 gm., or about eleven and one-half times that of the first day. As these figures indicate, a curve of the average capacity in the first ten days (Curve B, Figure 1) shows two distinct segments. During the period from birth to the fifth day it rises rapidly, thereafter it is continued upward at a much less rapid rate.

TABLE 2.—AVERAGE CAPACITY OF THE STOMACH IN THE FIRST TEN DAYS OF POSTNATAL LIFE

Days	Average Physiologic Capacity (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	5	6	6	8	5	7
2	10	13	13	14	11	13
3	22	27	27	27	26	27
4	36	42	45	51	46	46
5	43	58	57	62	59	57
6	43	59	64	72	70	64
7	48	60	67	76	79	68
8	51	66	71	78	80	71
9	55	68	75	83	87	76
10	60	72	79	90	96	81

Average maximum physiologic capacity.—In this study the average maximum physiologic capacity has been determined by adding the sums of the largest meal ingested by each child of the series on a given day and dividing the result by the number of cases. This is a somewhat different measurement from that employed by Feer[14] and by Scammon,[11] who used the maximum meal of a given week as a basis for determining the average maximum. The value as determined by the above definition is shown in Table 3 and is represented graphically by curve "A" in Figure 1.

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14. Feer, E.: Beobachtungen über die Nährungsmengen von Brustkindern, Jahrb. f. Kinderh. 42:195, 1896.

Examining these figures and the graph it is seen that there is a close relationship between average and average maximum capacity. The average maximum capacity on the first day is 9 gm. This is more than doubled on the second day (22 gm.) and increases nearly fivefold on the third day (43 gm.). On the fourth day it is a little more than seven times as great as on the first day. Thereafter, as in the case of the average capacity, the gain is much slower and on the tenth day it is eleven and two-thirds times that of the first day, or 105 gm.

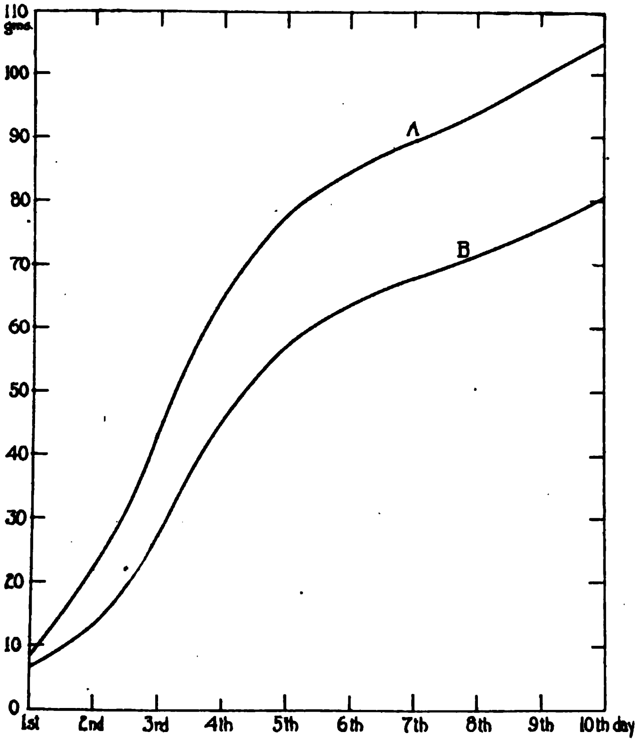

Fig. 1.—A graph showing the physiologic capacity of the stomach in the first ten days of postnatal life. A, curve of average maximum physiologic capacity; B, curve of average physiologic capacity. Based on all cases having a birth weight of 2,000 gm. or more.

The curve illustrating the changes in average maximum capacity (Curve A, Figure 1) is almost a duplicate of that of the average capacity, although all of the values are somewhat greater. It shows the same two phases as does the curve of average capacity.

Relative average and average maximum physiologic capacity.—Some interesting results are obtained if the average physiologic capacity and the average maximum capacity are calculated in terms

TABLE 3.—Average Maximum Physiologic Capacity of the Stomach in the Ten Days of Postnatal Life

Days	Average Maximum Physiologic Capacity (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	7	9	9	10	6	9
2	18	22	23	24	19	22
3	35	41	43	45	44	43
4	53	60	65	71	65	65
5	58	70	78	85	85	78
6	63	78	86	94	88	85
7	64	82	91	98	100	90
8	65	86	94	105	100	94
9	81	87	99	107	114	99
10	84	92	104	115	122	105

TABLE 4.—Average Physiologic Capacity of the Stomach in the Ten Days of Postnatal Life, Calculated in Per Cent. of the Body Weight at Birth

Days	Average Physiologic Capacity in Per Cent. of the Body-Weight at Birth					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	0.23	0.23	0.22	0.23	0.18	0.21
2	0.44	0.45	0.39	0.38	0.26	0.39
3	0.97	0.94	0.83	0.74	0.63	0.81
4	1.61	1.47	1.40	1.38	1.11	1.38
5	1.92	1.87	1.76	1.66	1.43	1.72
6	1.90	2.08	1.97	1.98	1.69	1.95
7	2.12	2.12	2.07	2.05	1.91	2.06
8	2.26	2.33	2.18	2.09	1.98	2.16
9	2.45	2.40	2.31	2.23	2.10	2.28
10	2.66	2.52	2.42	2.42	2.38	2.43

TABLE 5.—Average Maximum Physiologic Capacity of the Stomach in the First Ten Days of Postnatal Life, Calculated in Percentages of the Body Weight at Birth

Days	Per Cent. of Body-Weight					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3.500 to 4,000 Gm.	4,000 Gm. or More	
1	0.29	0.32	0.27	0.28	0.14	0.27
2	0.80	0.79	0.70	0.64	0.47	0.68
3	1.54	1.46	1.31	1.22	1.06	1.29
4	2.35	2.13	2.00	1.92	1.57	1.96
5	2.57	2.46	2.40	2.28	2.06	2.35
6	2.80	2.75	2.65	2.58	2.14	2.58
7	2.84	2.89	2.79	2.68	2.42	2.73
8	2.87	3.05	2.90	2.80	2.42	2.85
9	3.59	3.08	3.06	2.87	2.75	2.99
10	3.71	3.25	3.22	3.08	2.95	3.17

of the body weight at birth. These figures are shown in Tables 4 and 5 and the curves shown in Figure 2 are their graphic expression. The average gastric capacity in the first day is equal to about one-fifth of one per cent. of the body weight. By the second day this has risen to about 0.8 per cent. and on the fourth day to nearly 1.4 per cent. of the birth weight. After the fourth day the relative gastric capacity, like the actual average capacity, increases more slowly. By the tenth day the average capacity is equal to about 2.4 per cent.

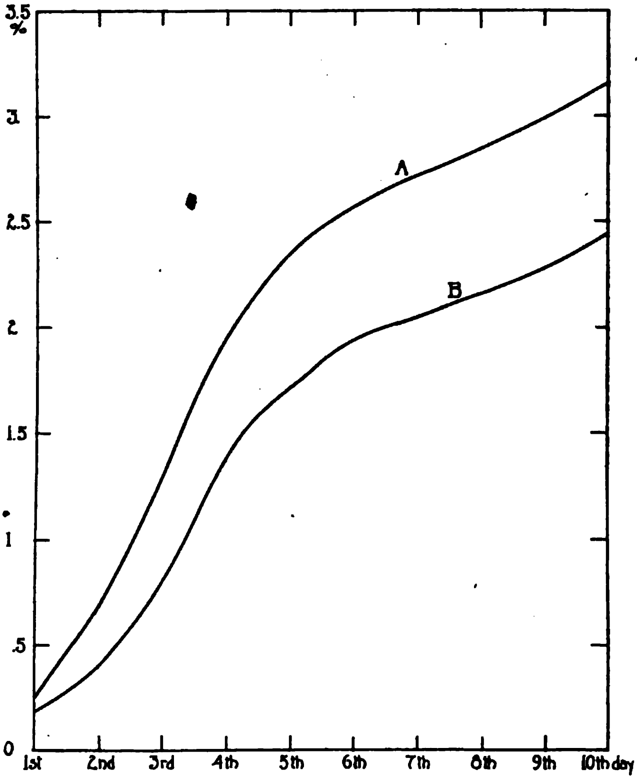

Fig. 2.—A graph showing the physiologic capacity of the stomach in the first ten days of postnatal life, as determined in per cent. of the body weight at birth. A, relative average maximum physiologic capacity; B, relative average physiologic capacity. Based on all cases having a birth weight of 2,000 gm. or more.

of the body weight at birth or about twelve times more than the average capacity on the first day.

The changes in the relative average maximum capacity are very similar to those in the relative average capacity. Starting at 0.27 per cent. on the first day, the relative average maximum rises rapidly to nearly 2 per cent. by the fourth day. Thereafter the amount increases much more slowly up to the tenth day, when it stands at nearly 3.2 per cent.

The curves based on these figures are much alike and are quite similar to those of the average and the average maximum capacity. They show the same characteristics of the rapid initial rise until the fourth day and the slower elevation from that point to the end of the period of observation (Fig. 2).

Relation between body weight and physiologic capacity.—The results which have been presented are based upon the study of the entire series of cases having a body weight of 2,000 gm. or over. The same data were studied further by arranging the cases into groups according to body weight at birth. Five of these groups were established: Group I, from 2,000 to 2,500 gm.; Group II, from 2,500 to 3,000 gm.; Group III, from 3,000 to 3,500 gm.; Group IV, from 3,500

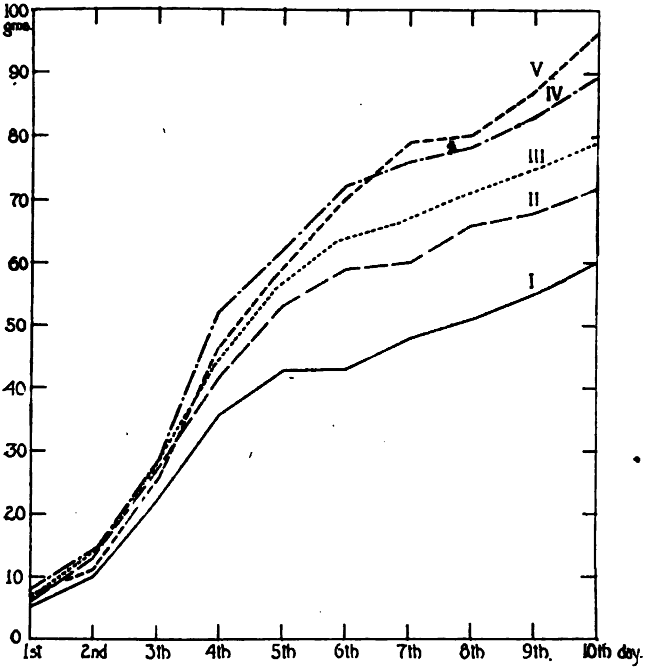

Fig. 3.—Average physiologic gastric capacity in the first ten days of postnatal life, in groups of children arranged according to birth weight. Curve I, average capacity of children with a birth weight of from 2,000 to 2,500 gm. Curve II, average capacity of children with a birth weight of from 2,500 to 3,000 gm. Curve III, average capacity of children with a birth weight of from 3,000 to 3,500 gm. Curve IV, average capacity of children with a birth weight of from 3,500 to 4,000 gm. Curve V, average capacity of children with a birth weight of 4,000 gm. or more.

to 4,000 gm. and group V, 4,000 gm. and over. The results obtained by this procedure are shown in Tables 2, 3, 4 and 5, and by the curves shown in Figures 3, 4, 5 and 6.

The absolute average gastric capacity evidently increases with the body weight in Groups I, II, III and IV (children weighing between 2,000 and 4,000 gm.). As will be seen in Table 2 and in Figure 3, there is a slight difference in favor of the groups of heavier children even on the first day and this becomes more noticeable in the latter part of the period. Group V (children having a birth weight of 4,000 gm. or over) shows a somewhat different condition. During the

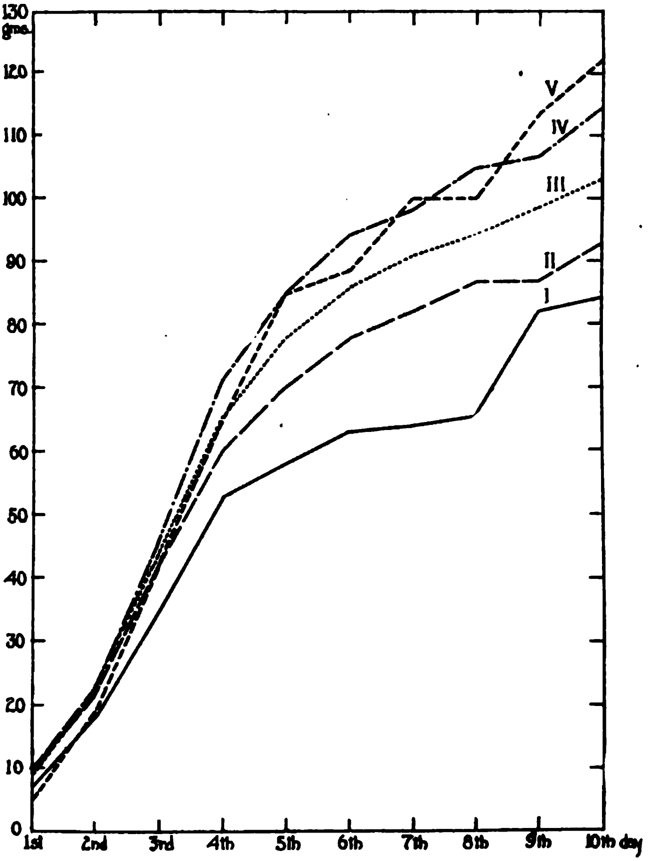

Fig. 4.—Average maximum physiologic gastric capacity in the first ten days of postnatal life, in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000 gm. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of from 4,000 gm. or more.

first three days of postnatal life the average capacity in these infants is slightly below that of the other groups of children and is only a little more than that of Group I (weighing from 2,000 to 2,500 gm.). However, the capacity of the heaviest group rises rapidly on the fourth and fifth days and on the sixth day and thereafter it exceeds that of any of the other groups.

The absolute average maximum capacity shows relations similar to those just described. It rises with the birth weight in all groups under 4,000 gm., but Group V (of 4,000 gm. and over) shows the lowest average maximum capacity on the first day. It is not until the ninth day that this value is greater in the heaviest than in the lighter groups of children.

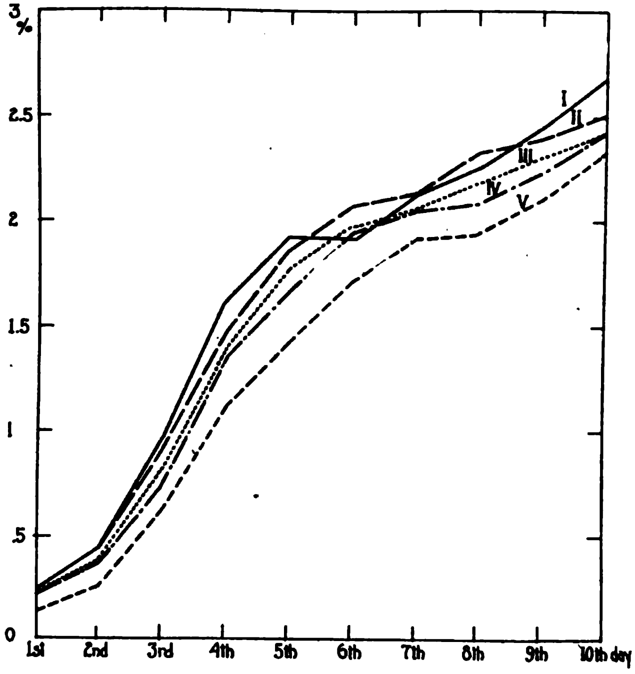

Fig. 5.—A graph illustrating the relative average physiologic gastric capacity in the first ten days of postnatal life in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of 4,000 gm. or over.

The figures on the *relative* physiologic capacity, i. e., the capacity as calculated in per cent. of the birth weight, show relations which are quite different from those of absolute physiologic capacity.

On the first day the relative average capacity is approximately the same in all groups of children having a birth weight under 4,000 gm. Thereafter, with one minor exception, the relative capacity is always greater in the lighter than the heavier groups. This difference, although not very great, is practically always present. The children of Group V (of 4,000 gm. and over) have a relative capacity only a little over one-half as great as that of the lighter groups and the average value always remains far below that of the other groups during the period of observation (Fig. 5).

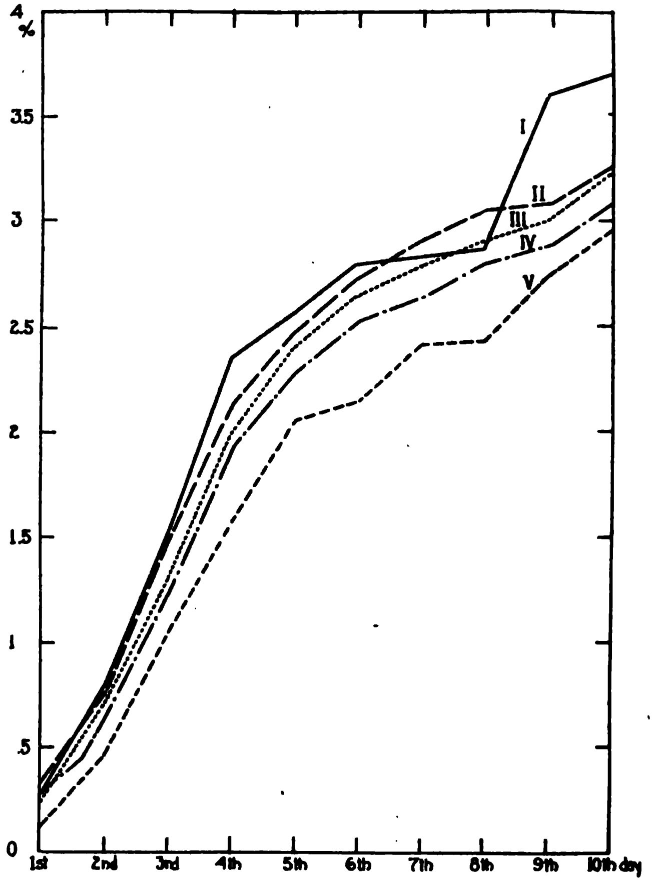

Fig. 6.—A graph illustrating the relative average maximum physiologic gastric capacity in the first ten days of postnatal life in groups of children arranged according to birth weight. Curve I, children having a birth weight of from 2,000 to 2,500 gm. Curve II, children having a birth weight of from 2,500 to 3,000 gm. Curve III, children having a birth weight of from 3,000 to 3,500 gm. Curve IV, children having a birth weight of from 3,500 to 4,000 gm. Curve V, children having a birth weight of 4,000 gm. or over.

The history of the relative maximum capacity is similar to that of the relative average capacity. The general rule that the smaller the birth weight of the group the larger the relative capacity holds true throughout except for the first day, when the relative maximum capacity is about the same in all groups of children under 4,000 gm. in weight, and for the eighth day, when this value in Group I (from 2,000 to 2,500 gm. in weight) falls below that of Group II (from 2,500 to 3,000 gm. in birth weight).

It may, therefore, be concluded that while the heavier children of this series tend to have a larger absolute physiologic capacity than do the lighter ones, this capacity does not increase directly in proportion with body size.

TABLE 6.—DIFFERENCES IN THE AVERAGE PHYSIOLOGIC GASTRIC CAPACITIES OF FIRST-BORN AND LATER CHILDREN *

Days	Differences in Capacities (Gm.)					
	Cases Having a Birth-Weight of					All Cases of 2,000 Gm. or More
	2,000 to 2,500 Gm.	2,500 to 3,000 Gm.	3,000 to 3,500 Gm.	3,500 to 4,000 Gm.	4,000 Gm. or More	
1	+1	—1	+1	+6	+6	0
2	0	+6	—3	+4	+7	+2
3	0	+9	—5	+4	+15	+3
4	0	+6	+1	+12	+23	+5
5	—4	+3	—4	+3	+6	—1
6	+7	—1	—10	—2	+17	—1
7	+5	—4	—13	+2	+20	0
8	+8	—3	—8	+3	+19	0
9	—2	—2	—5	+2	+34	+3
10	—13	+4	—3	0	+13	+3

* Figures preceded by a minus sign indicate a greater average capacity in first born children. Figures preceded by a plus mark indicate a greater average capacity in later children.

Physiologic capacity in first-born and later children.—The average and the relative average physiologic capacity were calculated separately for first-born and for later children. This was done first for the entire series of cases and then for the several groups arranged according to birth weight. The differences between the first born and later children were then determined from these figures and are shown in Table 6. The figures in this table which are preceded by a plus sign indicate an excess in capacity of the later children over the first born, and those preceded by a minus, an excess in capacity of the first born over the later born. If Groups I to IV, inclusive, of this table are examined, it will be seen that there are no consistent differences in these values in the two classes of children. However, in Group V, having a birth weight of 4,000 gm. or over, the capacities of later children are consistently and considerably greater than those of first born infants. As the relative average capacities showed practically identical results they will not be considered here in detail.

Physiologic capacity in males and females.—The average and the average maximum capacities were determined separately for males and for females in Group III (children having a birth weight of from 3,000 to 3,500 gm.). No consistent sex difference in capacity, as determined by either of these measures, was observed.

Variability in average physiologic capacity in the neonatal period.—It is, of course, well known that the variation in the amounts ingested at single meals by young infants is very great, but apparently no attempt has been made to measure it. In order to secure some measure of this value we determined the range of variation and the average deviation and the percentage deviation in the feeding records of the group of children having a birth weight ranging from 3,000 to 3,500 gm. (Group III).

The range of variation is easily secured by determining the maximum and minimum meal of the entire series of feeding records for each day of the period of observation. This determination, while of interest, tells us little of the actual amount of variation in our material, which is much better indicated by the average deviation and the percentage deviation. The average deviation is calculated by first determining the amount that each observation differs from the average of the whole series. These amounts are then added (plus and minus signs being disregarded) and the sum is divided by the total number of cases. The result expresses the average deviation (in this case in grams). This value can be readily converted into a per cent. of the average capacity by dividing by the average of all cases and multiplying by 100.

TABLE 7.—VARIABILITY IN AVERAGE PHYSIOLOGIC GASTRIC CAPACITY IN IN THE FIRST TEN DAYS OF POSTNATAL LIFE*

Days	Number of Observations	Average Capacity, Gm.	Minimum Feeding, Gm.	Maximum Feeding, Gm.	Average Deviation, Gm.	Per Cent. Deviation
1	154	6	3	60	3.6	60.0
2	698	13	4	80	6.8	52.3
3	718	27	3	110	15.2	56.3
4	718	45	5	180	17.9	39.8
5	712	57	8	140	19.2	34.7
6	714	64	2	165	19.3	30.1
7	714	67	10	145	20.6	30.7
8	710	71	10	160	21.3	30.0
9	700	75	5	148	20.5	27.3
10	614	79	10	210	20.6	26.0

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* Based upon the feeding records of children with a birth-weight ranging from 3,000 to 3,500 grams.

The results of these calculations are shown in Table 7 and are, in part, graphically expressed in Figure 7. The minimum meal during the first ten days ranges from 2 to 10 gm. and shows no particular regularity. The maximum meal was 60 gm. on the first day and rises fairly steadily to 160 gm. on the sixth day. Thereafter it is quite irregular. The average deviation rises rapidly in the first three or four days, but after the fourth day it stands between 19.2 and 21.3 gm., which is surprisingly constant considering the nature of the material. The percentage deviation in the first three days of postnatal life forms over one-half of the average capacity. It then decreases, at first rapidly and later quite slowly, during the remainder of the period. In round numbers the percentage variability in the first third of the period of observation is twice as great as in the last third.

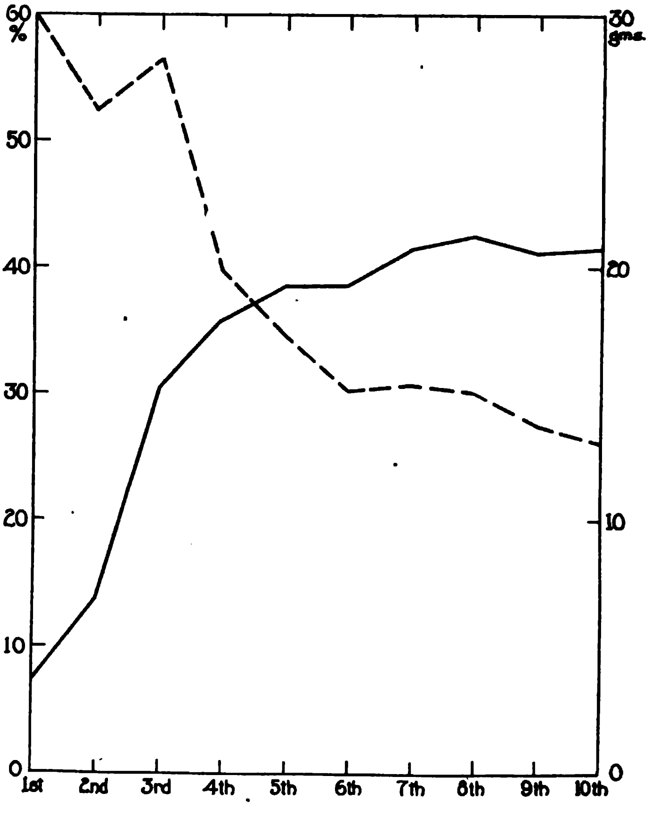

Fig. 7.—A graph illustrating the changes in variability in average physiologic gastric capacity in the first ten days of postnatal life. Curve A (in solid line), average deviation in average physiologic capacity. Curve B (in broken line), percentage deviation in average physiologic capacity. Based on the feeding records of a group of 143 children having a birth weight ranging from 3,000 to 3,500 gm.

This variability seems to have no close relation to the feeding schedule of the children. The maximum meal of the day may occur at any of the five feeding periods. In the first four days it is less frequently the first meal in the morning, while in the last six days the last meal in the evening is less often the largest one of the day. However, the differences in distribution of the maximum meal among the several feeding periods in the entire group of cases are so slight that no definite conclusion can be drawn from them.

In our entire series of cases there were forty-six instances in which a meal was missed. In eighteen cases the succeeding meal was smaller than the average; in twenty-two cases it was larger than the average, and in six cases it was the same as the average meal. The small amount of data which we have on this subject does not indicate that loss of a meal is compensated for by a larger succeeding one. in the first few days of postnatal life.

Percentage increment in physiologic capacity in the neonatal period.—The measures of growth in gastric capacity which have been described in the preceding sections of this paper are mainly in the form of absolute quantities. A much more striking exposition of the changes is given by the daily percentage increment. This value is calculated by determining the gain in capacity for each day in per cent. of the capacity of the day preceding. The results of these calculations are shown in graphic form in curves B and C in Figure 8. The increment in average physiologic capacity is over 80 per cent. on the second day and over 100 per cent. on the third day. Thereafter, it falls rapidly to about 20 per cent. on the fourth day and to less than 10 per cent. for the last third of the period of observation. The percentage increment in maximum physiologic capacity follows much the same history although it is greater at the beginning of the period (Curve B, Fig. 8).

Relation of average physiologic capacity to average maximum physiologic capacity in the neonatal period.—In a recent paper one of us pointed out that the average maximum physiologic capacity, from the third week after birth until the seventh month, is about one-half greater than the average physiologic capacity. The relation of these two values in the period of the new-born shows several striking changes. On the second day the average maximum capacity is about 25 per cent. greater than the average capacity. On the second day it is 70 per cent. greater. It then drops until the fifth or sixth day to about one-third more than the average capacity (Curve A, Fig. 8.).

The anatomic capacity of the stomach in the new-born and the neonatal period.—The anatomic capacity of the stomach in the new-born, as determined by a number of observers using a variety of methods, falls between 25 and 35 c.c. Most of the published work on anatomic capacity at birth does not include records of the individual cases and therefore is not very satisfactory. The most complete published data on this subject are those of Alliot,[10] and to these we have been able to add a small number of personal observations. The combined data available to us are shown in Table 8. The average anatomic capacity in a series of 25 new-born children ranging in birth weight from 2,000 to 4,300 gm. was 33 cc. In thirteen premature children having a birth weight ranging from 1,200 to 2,000 gm. the average capacity was 22 c.c. In new-born children having a body weight between 2,000 and 3,000 gm. the average capacity was 30 c.c.; and in those between 3,000 and 4,000 gm. body weight, 35 c.c. Three very large infants, having a body weight of 4,000 gm. or more, had an

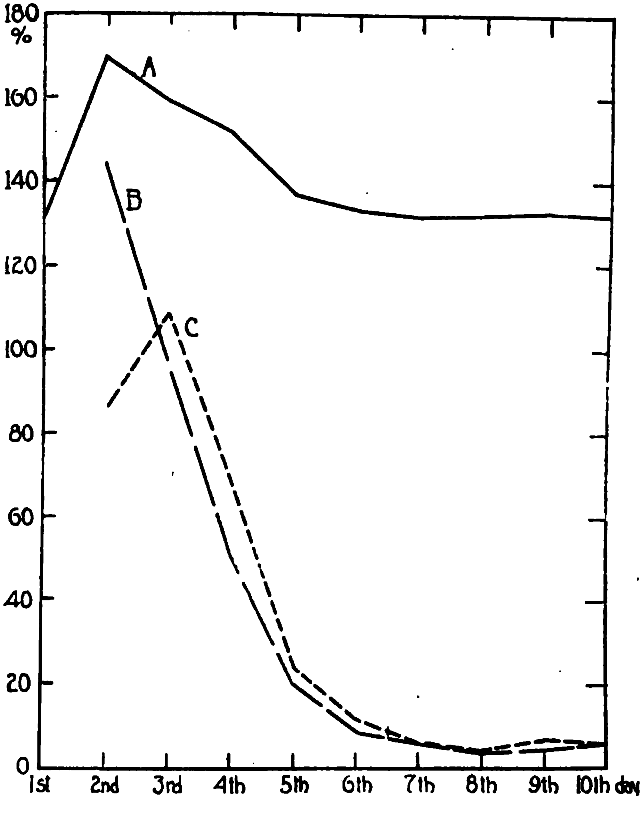

Fig. 8.—Curve A, percentage which the average maximum physiologic capacity forms of the average physiologic capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over. Curve B, percentage increment in the average physiologic gastric capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over. Curve C, percentage increment in the average maximum physiologic gastric capacity in the first ten days of postnatal life. Based on all cases of 2,000 gm. and over.

average capacity of 38 c.c. Thus the anatomic capacity at birth appears to increase somewhat with the body weight as does the physiologic capacity of the neonatal period.

The relative anatomic capacity, i. e., the capacity of the stomach calculated in per cent. of the body weight (c.c. considered equivalent to gm.), was, for this same series of cases, 1.3 per cent. in infants having a body weight below 2,500 gm,, 1.1 per cent. in children weighing between 2,500 and 3,500 gm., and 0.9 per cent. in children weighing 3,500 gm. or more. Thus the relative anatomic capacity of the stomach decreases as the body weight increases, as does the relative physiologic capacity in the neonatal period.

TABLE 8.—AVERAGE ANATOMIC CAPACITY OF THE STOMACH IN THE NEW-BORN AS DETERMINED BY ZUCARRELLI'S METHOD

Range of Body-Weight, Gm.	Average Body-Weight, Gm.	Number of Cases	Average Anatomic Capacity, C.c.
1,500 to 2,000	1,710	13	22
2,000 to 2,500	2,140	8	30
2,500 to 3,000	2,740	7	30
3,000 to 3,500	3,210	6	35
3,500 to 4,000	3,710	6	35
4,000 or more	4,340	3	38
2,000 or more	3,140	25	33

Detailed observations on the anatomic capacity of the stomach in the period between birth and the end of the second postnatal week are not very numerous. The average anatomic capacity of the first week, as indicated by the data of Fleishmann,[15] Froloffski,[16] Stössl,[17] Zuccarelli [18] and Rotch,[19] is approximately 45 c.c. or nearly one-third more than the capacity at birth. In the second week the data collected by these same observers and by Holt,[20] d'Astros,[21] Politzer,[22] Muggia [23] and others, indicate that the anatomic capacity is about 75 c.c. These figures are based on determinations by a variety of methods, although the majority of observations were made with Zuccharelli's method. The curve of growth in anatomic capacity in the neonatal period is

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15. Fleischmann: Klinik der Pädiatrik, Wien., 1875.

16. Froloffski: Material on the Anatomy of the Digestive Tract in Sucklings, Diss., St. Petersburg, 1876.

17. Stössl: Semiotik des Kindesalters, 1875.

18. Zuccarelli, P.: L'estomac de l'enfant, Thèse, Paris, 1894.

19. Rotch, T. M.: Pediatrics, Ed. 1, Philadelphia, 1896, p. 76 et seq.

20. Holt, L. E.: Observations on the Capacity of the Stomach in Infancy, Arch. Pediat. 7:960, 1891.

21. d'Astros: L'estomac de l'enfant; sa dilatation, Rev. de Mal. de l'enf. 12, 1894.

22. Pollitzer: Ideen zur Behandlung einer wissenschaftlichen Diatetik, Jahrb. f. Kinderh. 4, 1858.

23. Muggia, A.: La capacité e la posizione del ventricalo nei bambini, Giorn d. r. Accad. di med. di Torino, Series 4 2:351, 1896.

shown in semidiagrammatic form in Figure 9. As will be seen from this figure, the anatomic capacity of the stomach appears to increase at a uniform rate throughout the period and there are no indications of two distinct phases of growth comparable with those seen in all of the graphs of physiologic capacity.

Although the growth of the anatomic capacity of the stomach in the neonatal period appears to be quite slow if compared with the growth in physiologic capacity, it is very rapid compared with the growth in fetal life. In the first week after birth the anatomic capacity increases more than it does in the entire last third of fetal life, and the absolute increase in the first two weeks of postnatal life is considerably greater than the entire prenatal growth.

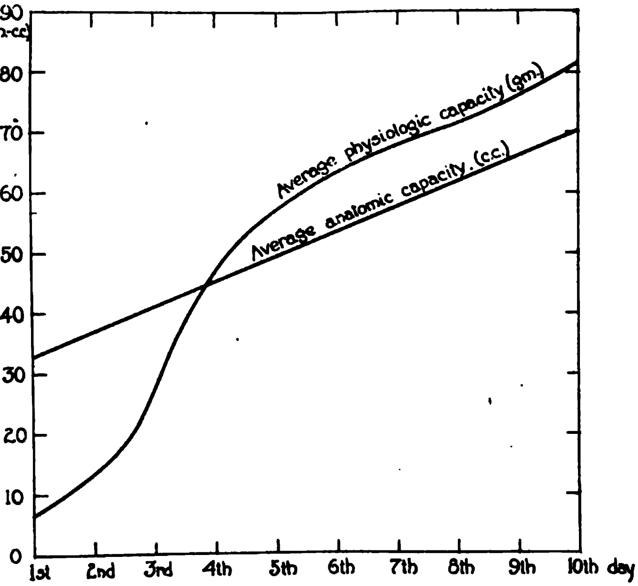

Fig. 9.—Semidiagrammatic curves illustrating the relation between the average physiologic capacity and the average anatomic capacity of the stomach in the first ten days of postnatal life.

DISCUSSION

The discussion of our data will be limited to a comparison of anatomic and physiologic capacity in the neonatal period and to a consideration of certain peculiarities of physiologic capacity during this time.

It has been pointed out by one of us (Scammon[11]) that during the greater part of the suckling period there is a close correlation between the anatomic capacity of the stomach, as determined postmortem, and the average physiologic capacity, as determined by weighing before and after feeding. The physiologic capacity, as determined by this method, was found to be approximately equal to the anatomic capacity of the organ under a pressure of between 15 and 20 centimeters of water. It was also noted that practically all of the technics used in determining anatomic capacity distend the viscus to about the same extent as does a pressure of 15 centimeters of water.

The relation between anatomic and physiologic capacity in the neonatal period is somewhat more complex than in the suckling period proper. It is represented in a semidiagrammatic fashion by the two curves shown in Figure 9. At birth the anatomic capacity of the stomach is roughly four and one-half times the physiologic capacity (on the average as 33 to 7). During the first half of the first week of postnatal life the anatomic capacity increases about one-third, while the physiologic capacity is increased about six-fold. The curves of these two measures of gastric capacity therefore converge and meet between the third and fourth day. Thereafter the anatomic capacity continues to increase at about the previous absolute rate. The physiologic capacity, however, rises much more slowly and is soon established slightly above that of the anatomic capacity. Evidently the constant relation which exists between the average physiologic and the average gastric capacity during the greater part of the suckling period is established during the middle part of the first week.

Taken as a whole, the figures on physiologic capacity which are presented here are distinctly higher than those of the earlier investigators mentioned at the beginning of this paper. This is not surprising considering that most of these workers made their observations upon infants which were fed eight or more times a day. The differences between our results and those of other recent observers are not very great.

The most noticeable feature of this series of observations is the marked change in physiologic capacity which takes place on the fourth or fifth day. This change is seen in all of the values of physiologic capacity which we have determined—in the absolute physiologic capacity both average and average maximum, in relative capacity, in percentage increments of both the average and the average maximum capacity, and in the two simple measures of variability which we have employed. In the first four days all measures of gastric capacity show a very rapid increase while in the last six days of the period of observation the increment is comparatively slow. In the first four days, also, the degree of variability in physiologic capacity is changing rapidly while in the latter part of the period it stands at a fairly constant figure.

The rapid gain in physiologic capacity of the first four days is probably no index of the actual growth of the stomach of this period since it is almost the end of this time before the physiologic capacity of the stomach equals the anatomic capacity. The figures and curves relating to this part of the period of observation are criteria of the ability of the mother to furnish food and of the ability of the infant to ingest it rather than actual measures of the growth of the stomach in cubic capacity. Similarly, the indices of variability which have been presented are measures of the variability of the above factors rather than of gastric capacity proper.

The later gain in physiologic capacity, from the fourth to the eleventh day, probably approaches much closer to the real index of the stomach's growth since it is substantially the same as the increase in anatomic capacity.

Unfortunately, we have no available data on the weight or surface area of the stomach in the first few days after birth to enable us to determine whether the growth of the organ in these respects is comparable with the changes in capacity. It is known, however, that the growth of the stomach in net weight is very great in the first postnatal months when the organ is increasing most rapidly in capacity.

As has been pointed out, our figures indicate that the absolute physiologic capacity increases, though not directly, with the birth weight of the child. This finding agrees with the earlier observations of Ssnitkin[5] on physiologic capacity. On the other hand, Holt[20] in his study of anatomic capacity, found no relation between this measure and body weight. However, his observations were made mainly on older children. That the relative physiologic capacity of groups of lighter children is greater than that of heavier groups has not, we think, been specifically pointed out previously, although several recent studies, such as those of Reicke[24] and Hammett,[25] have noted a relatively rapid rate of growth of premature infants which might be expected to be associated with a greater relative food intake. There are few published figures on the relative gastric capacity in the neonatal period. The only ones based on an extensive series of cases are those of Ssnitkin,[5] who calculated that the average meal was equal to 1 per cent. of the body weight plus 1 gm. for each day of postnatal life. This rule gives values far below those quoted in our tables despite the fact that our percentages are figured on the birth weight rather than the actual weight at the time of feeding. This discrepancy is probably due in part to the feeding methods employed in Ssnitkin's cases, and in part to the fact that his observations extended over the entire first month while ours were limited to the first ten days of postnatal life.

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24. Reicke, A.: Das Wachtum der Frühgeburten in den ersten Lebensmonaten, Ztschr. f. Kinderh. **13**:332, 1915.

25. Hammett, F. S.: The Relation Between Growth Capacity and Weight at Birth, Am. J. Physiol. **45**:396, 1918.

Our figures show no constant differences in the physiologic capacity of first born and later children, except for the group of heaviest cases. This result was unexpected for a priori one might expect that first born children would take smaller meals than later ones both because of greater birth trauma, which would limit their power of nursing, and because the mammary glands of primiparae begin to function a little later after delivery than do those of multiparae. While the difference in this later factor in multiparae and primiparae is one of hours only, according to Landois'[9] observations, still one might expect it to affect our averages slightly. It may be that our findings in this particular are due to the nature of the material studied, for it is the practice of the University Hospital to receive all primiparae for delivery while multiparae are only received when there is record of previous difficult deliveries, when pathologic symptoms are observed, or when the social conditions of the mother are adverse. By far the larger number of multiparous mothers of our series were admitted to the hospital for delivery because of adverse social circumstances. Possibly these circumstances have influenced the physical condition of the mothers to the extent of limiting the milk supply during the first ten days postpartum.

The group of heaviest children in our series (those having a birth weight of 4,000 gm. or more) show several peculiarities of gastric capacity not seen in the groups of smaller infants. These heavier children have smaller relative anatomic capacities at birth than do the lighter ones and their physiologic capacities, both absolute and relative, are smaller in the first week of life. In the early part of the second week the absolute physiologic capacity in this group rises above that of the lighter groups of children but the relative physiologic capacity remains far below throughout the period of observation. In this group, also, parity has a distinct effect on physiologic capacity, and the averages of first born children are distinctly below those of later children. We are inclined to attribute most of these peculiarities in physiologic capacity to the greater trauma which these children undergo at birth.

SUMMARY

The results of this study may be summarized as follows:

1. The average physiologic capacity of the stomach in the first day after birth is about 7 gm. This practically doubles in the second day, quadruples on the third, and increases almost sevenfold on the fourth. After the fourth day, the increase is much slower and the average capacity on the tenth day is 81 gm. or over eleven times that of the first day. The average maximum physiologic capacity increases in much the same manner as the average physiologic capacity.

It is about one-fourth greater than the average physiologic capacity on the first day and about two-thirds greater on the second. Thereafter the difference between the two measures decreases rapidly until the sixth day. After the sixth day the average maximum capacity remains about one-third more than the average capacity.

2. The relative physiologic capacity increases in much the same way as the absolute physiologic capacity. It is equal to 0.21 per cent. of the birth weight of the body on the first day, to 1.38 per cent. on the fourth day, and 2.43 per cent. on the tenth day. The relative maximum capacity is equal to 0.27 per cent. of the initial body weight on the first day, to 1.96 per cent. on the fourth day, and to 3.17 per cent. on the tenth day.

3. In the first ten days parity has no constant effect on the physiologic capacities of children having an initial body weight of from 2,000 to 4,000 gm. Sex has no effect on the physiologic capacity in this period.

4. The average deviation in physiologic capacity rises rapidly from the first to the fourth day. Thereafter it increases very slowly. The percentage deviation decreases rapidly until the fifth day and thereafter continues to drop very slowly.

5. All indices of physiologic capacity indicate that there is a distinct change in the nature of this value about the fourth day. Until this time the increase in capacity, in whatever manner it is calculated, is very rapid, thereafter it is much slower. In the first four days average deviation in capacity is increasing rapidly and percentage deviation is decreasing rapidly. After this time both of these measures change very little.

6. The anatomic capacity of the stomach at birth averages 33 c.c. This is increased about one-third in the first three or four days and is a little more than doubled in the second week. There is no indication of two definite stages in the development of anatomic capacity in the neonatal period corresponding to the two phases of physiologic capacity. Anatomic capacity and physiologic capacity approximate one another about the fourth day. Thereafter physiologic capacity runs parallel to the anatomic capacity but is slightly greater. This agrees with previous findings regarding this relation throughout the greater part of the suckling period.

7. The curve representing average physiologic capacity in the first ten days of post natal life shows two phases. The first segment, extending from birth to the fourth day, shows little relation to the actual capacity of the organ but is rather a measure of the ability of the average mother to furnish nourishment in this period and the ability of the average child to receive it. The second segment, extend-

ing from the fourth to the tenth day, is probably a fair measure of the actual increase in gastric capacity comparable with similar measures of this value made at later times in the sucking period.

8. The gastric capacities of children weighing 4,000 gm. or over at birth are somewhat different from those of infants of lighter weights. Both the average and the average maximum physiologic capacities of this group are smaller than those of lighter children in the first three or four days of post natal life but these values increase rapidly in the fifth and sixth days and before the end of the period exceed those of smaller infants. Parity has a slight but distinct effect on physiologic capacity in this group of large infants, and first born children have a smaller capacity than do the later born. The anatomic capacities of children of this group are somewhat greater absolutely but smaller relatively than in children of the lighter groups.

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Changes in the Form and Dimensions of the Chest at Birth and in the Neonatal Period

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MINNEAPOLIS

CHANGES IN THE FORM AND DIMENSIONS OF THE CHEST AT BIRTH AND IN THE NEONATAL PERIOD*

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In the fortnight following birth, the form and dimensions of the thorax undergo a series of peculiar changes which are dependent on a number of different factors. One of these changes, the increase in the horizontal circumference of the chest accompanying the first inspiration, is well known, but others, which are less marked and more variable, have apparently passed unnoticed. The following account of the changes in the form of the thorax of the new-born is based on measurements of the thoraces of late fetuses and full term still-born children, on observations of living infants on the first, third, fifth, seventh, tenth and twelfth days after birth, and on a number of observations on the horizontal chest circumference immediately before and after the first inspiration. The observations on the dimensions of the fetal thorax were made by Dr. L. A. Calkins as a part of an extensive study on the development of the proportions of the body in prenatal life, and our thanks are due him for permission to use these valuable data in the present investigations. The study on living infants was made at the Minneapolis General Hospital. In our study it proved impracticable to make thoracic measurements of the new-born until ten or fifteen minutes after birth and we have, therefore, made use of the excellent series of observations of Linzenmeier for data on the circumference of the chest immediately before and after the first inspiration.

Changes in the Horizontal Chest Circumference.—The horizontal circumference of the chest is usually determined at the level of the nipples, at the level of the lower end of the sternum, or at the tenth rib. Our study was based on measurements at the nipples and at the tenth rib. As the results of these measurements are not identical they will be considered separately.

The changes in the chest circumference at the level of the nipples are shown in Table 1 and in graphic form in Figures 1, 2 and 3. They are best presented by Figure 1, which is a semischematic curve showing the entire series of modifications in this dimension from late fetal life until the close of the second week after birth. Four phases may be recognized in this curve. The first phase, which includes the latter part of fetal life, is characterized by a slow increase in chest circumference directly proportional to the growth of the body in length and without any marked changes in rate of growth. The second phase is inaugurated with the first inspiration. Within the first few minutes after birth, and often with the first breath, the chest cicumference increases about 2 cm., or approximately 8 per cent. This period of rapid increase is a transitory one for, as a rule, before the close of the first twelve hours a third phase, one of circumference decrease, begins and this continues for two or three days thereafter. The final phase, one of circumference recovery, sets in on the third or fourth day, and by the latter half of the second week the thorax has regained the circumference which obtains immediately after the first inspiration.

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* This study was carried out with aid of a grant from the Research Fund of the University of Minnesota.

1. Linzenmeier, G.: Der Verschluss des Ductus arteriosus Botalli nach der Geburt des Kindes, Ztschr. f. Geburtsh. u. Gynäk. **76**:242, 1914.

TABLE 1.—CHANGES IN THE HORIZONTAL CIRCUMFERENCE OF THE CHEST (AT THE LEVEL OF THE NIPPLES) AT BIRTH AND IN THE NEONATAL PERIOD

Age	Number of Cases	Average Circumference, Cm.	Average Circumference in Per Cent. of the Chest Circumference 15 Min. after Birth
Birth (before first inspiration)	40	29.3*	93.9
15 minutes after birth.........	36	31.2	100.0
12 hours after birth............	36	30.7	92.8
3d day after birth.............	36	29.7	97.1
5th day after birth............	34	30.2	97.7
7th day after birth............	31	30.3	98.0
10th day after birth...........	19	30.5	98.8
12th day after birth...........	6	31.2	100.8

* Calculated from the data of Linzenmeier

The modifications in the circumference of the chest at the level of the tenth rib are shown in Table 2 and in Figures 2 and 3. In later fetal life the circumference at this level, like that at the nipples, increases slowly and steadily at a rate directly proportional to the growth of the body in length. We have no direct data on the changes in the tenth rib circumference with the establishment of respiration, but judging from the changes in the diameters of the chest at this level, there is some increase in circumference although not as much as at the level of the nipples. The later postnatal changes in the tenth rib circumference are very similar to those in the nipple circumference. From the first to the fourth or fifth day, there is a period of circumference decrease. This is followed by a second period of slow increase, the initial circumference following the establishment of respiration being regained about the tenth or twelfth day (Fig. 2).

The postnatal decrease in chest circumference does not seem to have been observed previously. This is not surprising, for the loss is generally small and would hardly be noticed unless systematic measurements were made day by day throughout the neonatal period on a considerable series of cases. The variability in the horizontal chest circumference at birth is considerable. Taylor[2] found that the standard deviation of the circumference at the nipples was 12.2 mm. for males and 17.7 mm. for females. With this degree of variation it is probable that the postnatal decrease would be entirely masked in any series of measurements taken at random at birth and in the neonatal period. While the reduction in chest circumference is often small, it seems to be fairly constant. Our measurements show some reduction at the level of the nipples in thirty-three of the thirty-six cases studied, and at the tenth rib in thirty-four cases. As is indicated in Tables 3 and 4, the variability in the amount of postnatal reduction is very great. The time of maximum reduction also differs considerably in various cases.

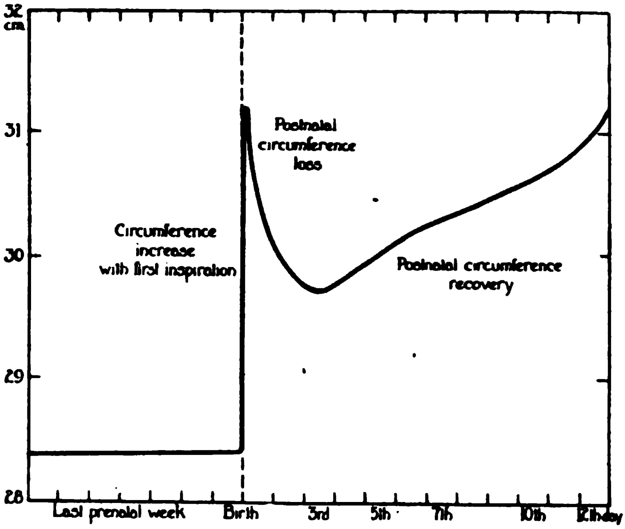

Fig. 1.—A semischematic curve illustrating the changes in the absolute circumference of the chest, at the level of the nipples, at birth, and in the first twelve days of postnatal life. Based on measurements of fetuses and still-born children and on observations on a series of living infants.

Since there is considerable individual variation in the circumference of the chest at birth, we have attempted to check the results of our absolute measurements by reducing these determinations to a percentage basis. This we have done by considering the circumference of the chest immediately after the establishment of respiration as 100 and calculating all later measurements as percentages of this initial one. This calculation was first made for each case separately and the individual percentages for each period of observation were then averaged. This procedure eliminates much of the error which is introduced in the average absolute dimensions by initial differences in size of the individual cases. The results of these calculations are given in the fourth columns of Tables 1 and 2 and are illustrated by the curves in Figure 3. These figures on the *percentage* loss and gain of the chest circumference in the neonatal period differ slightly from those obtained from the averages of the absolute dimensions, but the general courses of the changes as determined by these two methods are in close agreement.

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[2] Taylor, R.: The Measurements of Two Hundred and Fifty Full-Term New-Born Infants, Am. J. Dis. Child. **27**:353 (April) 1919.

The causes of these changes in chest circumference seem to be diverse. The increase in the later part of fetal life reflects the general growth of the tissues and organs of the thorax and probably, in particular, the formation of new lung alveoli, which is very active in this period. The sudden increase at birth no doubt corresponds, in the main, to the initial enlargement of the thorax which takes place at the establishment of respiration and which is accompanied by the partial expansion of the lung alveoli. It is possible that the dilation of the vascular bed of the lungs, following the close of the ductus arteriosus and the complete establishment of the pulmonary circulation, is also represented in this increase. The postnatal loss in circumference, on the other hand, seems to have nothing to do with the expansion of the lungs. In all probability, it is to be interpreted as another manifestation of the postnatal loss in mass of the infant, and, particularly, as an indication of the loss of fluid from the superficial tissues of the chest wall.

TABLE 2.—CHANGES IN THE HORIZONTAL CHEST CIRCUMFERENCE (AT THE LEVEL OF THE TENTH RIB) IN THE NEONATAL PERIOD

Age	Number of Cases	Average Circumference, Cm.	Average Circumference in Per Cent. of the Chest Girth Immediately after Birth
15 minutes after birth	36	31.4	100.0
12 hours after birth	36	30.5	97.4
3d day after birth	36	29.5	96.6
5th day after birth	34	30.5	96.8
7th day after birth	31	30.8	97.8
10th day after birth	17	30.7	97.6
12th day after birth	11	31.0	100.9

The changes following the phase of postnatal circumference decrease seem dependent on several factors. The enlargement of the thorax with the completion of the expansion of the lungs is probably the most important of these. The studies of a number of observers, and, particularly, the extensive observations of Gedgovd[3] have shown that all parts of the lungs are not fully expanded at the first inspiration or even in the first few days, but that it is often a week or more before all of the alveoli are even partially dilated. And the investigations of Ridella,[4] as well as the older data of de la Croix[5] and Rossignol[6] indicate that this initial dilatation of the alveoli is not a complete one. These conclusions are supported by the careful micrometric studies on the lungs of fetal and new-born animals by Addison and Howe.[7] It seems, then, that the volume of the lungs (and, therefore, the internal dimensions of the thorax) are normally increasing throughout the neonatal period, but that the effect of this increase on the external dimensions of the thorax is obscured in the first few days after birth by the more extensive decrease in the superficial soft parts of the chest wall which is associated with the postnatal weight loss. The effect of the continued increase in the volume of the lungs and thoracic cavity is pictured in the rise of the curve of the chest circumference which occurs in the latter part of the neonatal period after the major portion of the post-

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[3] Gedgovd, V. A.: Anatomical Peculiarities of the Respiratory Organs in Childhood, Diss. St. Petersburg, 1900.

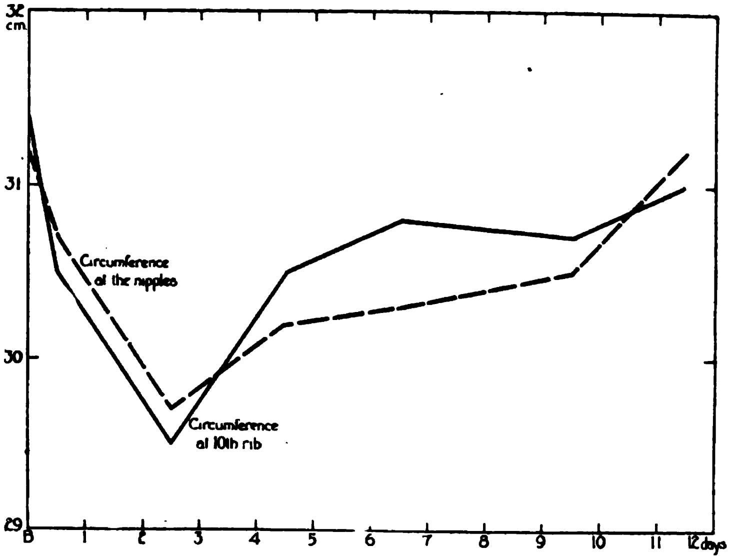

Fig. 2.—A graph illustrating the changes in absolute chest circumference, at the nipples and at the tenth rib, in the first twelve days of postnatal life. Based on measurements of a series of thirty-six children.

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[4] Ridella, A.: Modificazioni che avvengo nel polmone prima o dopo la nascita in relazione colla funzione respiratoria, Folia Gynaecol. **7**:421, 1912.

[5] de la Croix, N. J.: Die Entwicklung des Lungenepithels beim menschlichen Fötus und der Einfluss der Atmung auf Dasselbe, Arch. f. mikr. Anat. **22**:93, 1883.

[6] Rossignol: Recherches sur la structure intime du pulmon de l'homme, Thèse, Bruxelles, 1846.

[7] Addison, W. H. F., and Howe, H. W.: On the Prenatal and Neonatal Lung, Am. J. Anat. **15**:199, 1913.

natal weight decrease has taken place or when the recovery in body weight begins. A comparison of the changes in chest circumference with those in body weight in certain of our cases seems to support this view, for we find that the circumference loss and body weight loss are often synchronous while the recovery of the initial chest circumference often does not coincide with the recovery in body weight, but takes place a little sooner or even while the body weight is stationary. Other minor factors, such as the enlargement of the mammary glands associated with the formation of "witches' milk," may also have a slight effect on the circumference at the nipples.

TABLE 3.—Extent of Postnatal Loss in Chest Circumference at the Level of the Nipples. (Calculated in Per Cent. of the Chest Circumference 15 Minutes After Birth.)

	Number	Per Cent.
Cases showing no loss in circumference	3	9
Cases showing a loss of less than 5 per cent.	14	39
Cases showing a loss of 5 to 10 per cent.	14	39
Cases showing a loss of 10 to 15 per cent.	4	11
Cases showing a loss of 15 per cent. or more	1	2

The postnatal changes in the circumference at the tenth rib are probably due, in the main, to the same factors which influence the circumference at the nipples. The neonatal reduction at the tenth rib is a little greater and the recovery a little slower than at the nipples, presumably because the enlargement of the lower part of the chest in connection with the expansion of the lungs is less marked. Another factor which may play a part in the reduction of the tenth rib circumference is the postnatal decrease in the size of the liver which has been described by Miura.[8] This author finds a decline in the mass of the liver after birth which may be attributed to the decrease in blood content of the liver following the interruption of the flow of placental blood to the organ with the closure of the umbilical vein.

TABLE 4.—Extent of Postnatal Loss in Chest Circumference at the Level of the Tenth Rib. (Calculated in Per Cent. of the Chest Circumference 15 Minutes After Birth.)

	Number	Per Cent.
Cases showing no loss in circumference	2	6
Cases showing a loss of less than 5 per cent.	10	27
Cases showing a loss of 5 to 10 per cent.	20	56
Cases showing a loss of 10 to 15 per cent.	4	11

Changes in the Diameters of the Chest.—The anteroposterior and transverse diameters of the thorax were measured at the nipples and at the tenth rib in our series of living children. The summarized results of these measurements are shown in Tables 5, 6, and 7 and are represented graphically by the curves in Figures 4 and 5.

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[8] Miura, M.: Die Gewichtsabnahme verschiedener Organe vom Neugeborenen, Notizen meiner physiologischen und pathologischen Forschung, No. 15, 1912.

The changes in the diameters of the chest at the level of the nipples and at the tenth rib are quite similar in the neonatal period. After breathing begins the anteroposterior and transverse diameters undergo a series of modifications in which three main phases may be recognized. Of these the first is a period of diameter decrease which begins after respiration is established and extends from twelve hours to three or four days thereafter. The second phase occupies the latter part of the first week and the beginning of the second. During this time the diameters may decline slightly, remain stationary, or show minor fluctuations which are probably without significance. In the third period, which falls in the middle or latter part of the second week, the diameters again begin to increase and their initial dimensions (as observed immediately after the establishment of respiration) are generally regained between the tenth and fourteenth day. Thus the changes in the diameters of the thorax in the neonatal period show the same general characters of postnatal loss and recovery which were found in connection with the circumferences of the chest.

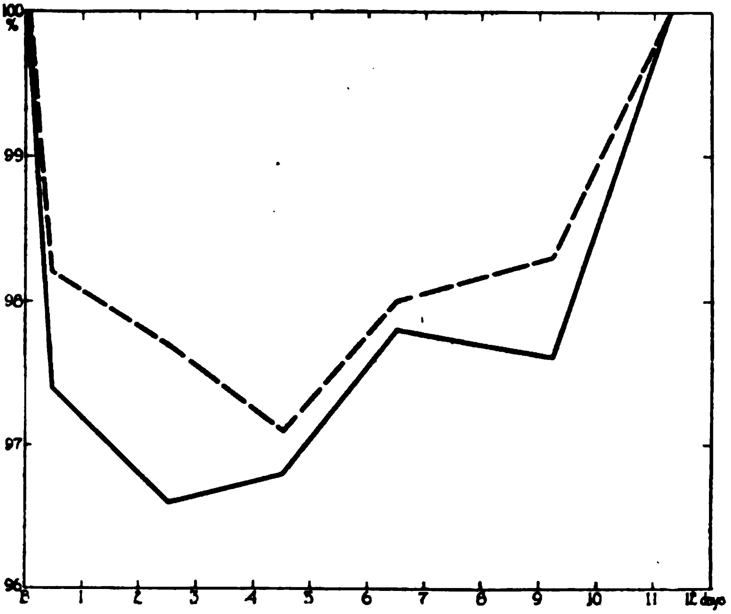

Fig. 3.—A graph illustrating the changes in the circumference of the chest at the level of the nipples and the level of the tenth rib. The circumferences for the first and later days are calculated in per cent. of the circumference of the chest ten to fifteen minutes after birth.

The postnatal reduction in the diameters of the chest is a fairly constant phenomenon. The anteroposterior diameter at the nipples showed a reduction in twenty-two of the twenty-three cases studied, and the transverse diameters in twenty cases. At the tenth rib the anteroposterior diameter was reduced in eighteen of twenty-three cases and the transverse diameter in twenty-two cases. The amount of reduction of the anteroposterior diameters is much greater both absolutely and relatively than the reduction of the transverse diameters. This is true of the diameters both at the level of the nipples and at the tenth rib. This difference, as well as the variation in reduction in individual cases, is shown in Tables 6 and 7. The causes of these changes will be considered in connection with the thoracic index.

Changes in the Thoracic Index.—The thoracic index is a value determined by dividing the anteroposterior diameter of the chest by the transverse diameter and multiplying the quotient by 100. The result gives the anteroposterior diameter of the thorax in the form of a per cent. of the transverse diameter, and is an expression of the relative depth of the chest. Thanks to the studies of Hutchinson,[9] Mehnert,[10] Rodes,[11] Jackson [12] and others the general course of the changes in the thoracic index in the developmental period is well known. It is very high (nearly 200) in the young embryo because of the large size and great anteroposterior diameter of the heart and liver; but with the development of the thoracic skeleton it gradually falls to less than 90 in the fetus at term. In childhood the index continues to decline, usually falling to about 70 in maturity. The index is markedly affected at birth by a number of factors. The course of the modifications of the

TABLE 5.—CHANGES IN THE DIAMETERS OF THE CHEST IN THE NEONATAL PERIOD

Age	Number of Cases	Average Diameters at the Nipples		Average Diameters at the Tenth Rib	
		Transverse	Anteroposterior	Transverse	Anteroposterior
15 minutes after birth	23	7.7	8.2	8.9	8.5
12 hours after birth	23	7.7	7.9	8.7	8.0
3d day after birth	23	7.5	7.7	8.8	7.9
5th day after birth	21	7.5	7.6	8.6	7.8
7th day after birth	18	7.5	7.7	8.8	8.0
10th to 12th days after birth	10	7.7	7.8	8.9	8.1

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[9] Hutchinson, W.: Some Deformities of the Chest in the Light of Its Ancestry and Growth, J. A. M. A. **29**:512, 1897.

[10] Mehnert, E.: Ueber topographische Altersveränderungen des Atmungsapparates, Jena, 1901.

[11] Rodes, C. B.: The Thoracic Index in the Negro, Ztschr. f. Morphol. u. Anthropol. **9**:102, 1906.

[12] Jackson, C. M.: Is Gravity the Factor Determining the Thoracic Index? Ztschr. f. Morphol. u. Anthropol. **10**:240, 1907.

thoracic index at the nipples in the neonatal period is shown in Table 8 and by Figure 6.

The changes in the index at the level of the nipples are shown in semischematic form in curve B of Figure 6. In the latter part of fetal life (ninth and tenth fetal months) the average index is about 86.[13]

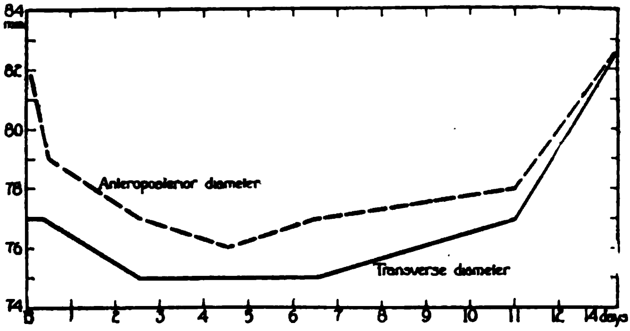

Fig. 4.—A graph illustrating the changes in the anteroposterior and transverse diameters of the chest, at the nipples, in the first twelve days after birth.

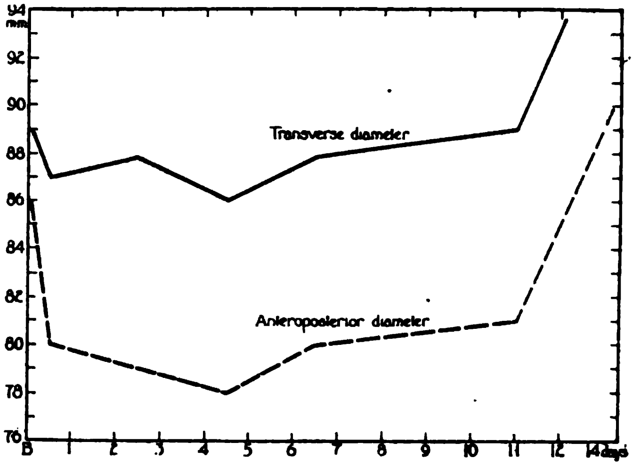

Fig. 5.—A graph illustrating the changes in the anteroposterior and transverse diameters of the chest at the tenth rib, in the first twelve days after birth.

At birth, with the establishment of respiration, it rises immediately to an average of 106. This initial rise is followed almost at once by a rapid decline, the index falling to an average of 102 within twelve hours after birth. During the remainder of the neonatal period, the measure drops

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13. This determination was made from Dr. Calkins' material and is not corrected for the changes which occur in the chest on injecting the cadaver. Dr. Calkins' observations show that these changes tend to increase the anteroposterior diameter more than the transverse, and that the true thoracic index in later fetal life is a little lower than is here recorded.

slowly and irregularly, being about 100.5 in the middle of the second postnatal week. Six months or more pass before it has declined to the average which obtains just before birth.

The changes in the index at the level of the tenth rib are similar in character but are less pronounced than those at the level of the nipple. They are presented semidiagrammatically by curve A of Figure 6. In the latter part of fetal life and in children who have not breathed, the average index at the lower level is 91 or 92. With the establishment of respiration, it rises to an average of 95 and then declines again, in the course of the first twenty-four hours, to 92. By the middle of the second postnatal week it has dropped to 86.

TABLE 6.—EXTENT OF POSTNATAL LOSS IN THE TRANSVERSE AND ANTEROPOSTERIOR DIAMETERS OF THE CHEST AT THE LEVEL OF THE NIPPLES

	Antero-posterior Diameter	Transverse Diameter
Number of cases showing no reduction	1	3
Number of cases showing a reduction of less than 0.5 cm.	1	8
Number of cases showing a reduction of between 0.5 and 1.0 cm.	9	8
Number of cases showing a reduction of between 1.0 and 1.5 cm.	11	4
Number of cases showing a reduction of between 1.5 and 2.0 cm.	1	0

The rise in the thoracic index which occurs immediately after birth presumably takes place at the first breath when the chest wall is carried upward and forward as in the inspiratory movements of later life. The causes of the decline of the index which follows this initial rise are more obscure. We are inclined to attribute the change, in part at least, to the effect of gravity on the form of the chest. During prenatal life the fetus is surrounded with fluid and consequently all external pressures are transmitted to its surfaces equally from all sides. Thus the tendency of all external pressures would be to mold the body into spherical form of which all diameters would be equal. But after birth, when the infant spends the greater part of the time prone on the back or abdomen, the force of gravity would be exerted on the anterior or posterior surfaces of the thorax, tending to decrease its anteroposterior diameter and to increase its transverse diameter. While it seems reasonable to regard

TABLE 7.—EXTENT OF POSTNATAL LOSS IN THE TRANSVERSE AND ANTEROPOSTERIOR DIAMETERS OF THE CHEST AT THE LEVEL OF THE TENTH RIB

	Antero-posterior Diameter	Transverse Diameter
Number of cases showing no reduction	1	5
Number of cases showing a reduction of less than 0.5 cm.	2	8
Number of cases showing a reduction of between 0.5 and 1.0 cm.	8	5
Number of cases showing a reduction of between 1.0 and 1.5 cm.	9	4
Number of cases showing a reduction of between 1.5 and 2.0 cm.	3	1

gravity as one of the important factors in the early reduction of the thoracic index, it is probable that the modifications in the forms of the chest which are due to this factor take place in a comparatively short time after birth. Jackson's experiments [12] indicate that gravity has little to do with the slow flattening of the chest which goes on in later infancy and childhood.

It is possible also that the dropping of the dome of the diaphragm after birth may have some effect on the thoracic index. That the diaphragm does descend in the thorax shortly after birth seems well established, but so little is known either of the extent or the time of this change that it is hardly possible to correlate it with the modifications in chest form.

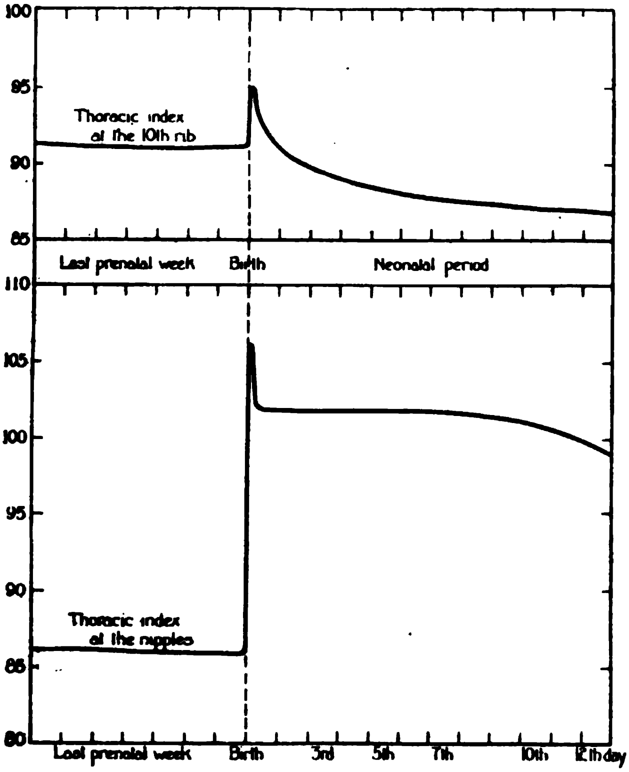

Fig. 6.—Two semischematic graphs illustrating the changes in the thoracic index at birth and in the neonatal period.

Whatever factors may be responsible for the modifications in the thoracic index in the neonatal period, these changes are correlated in an interesting manner with the internal changes of the lungs. It was pointed out by Champneys [13] a number of years ago that the inflation of the lungs does not take place at the same rate in all parts of these organs. He found that the anterior surfaces and medial margins were expanded distinctly before the lateral portions and the inferior margins.[15] Thus the early expansion of the anterior surfaces and medial margins of the lungs reflects the early increase in the anteroposterior diameter of the thorax, particularly at the level of the nipples, while the subsequent expansion of the lateral portions corresponds to the later increase in the transverse diameters. And, similarly, the expansion of the lower portions and inferior margins is considerably delayed in correspondence with the slower and smaller changes in the circumference and thoracic index at the level of the tenth rib.

SUMMARY

At birth and in the neonatal period the thorax undergoes a series of modifications in dimensions and form which may be summarized as follows:

TABLE 8.—CHANGES IN THE THORACIC INDEX AT BIRTH AND IN THE NEONATAL PERIOD

Age	Number of Cases	Average of Indices	
		At the Level of the Nipples	At the Level of the Tenth Rib
9th fetal month	18	86.5	92
10th fetal month	13	86.0	92
Birth (full-term fetuses)	19	86.0	91
15 minutes after birth	23	106.0	95
1st day (12 hours) after birth	23	102.0	92
3d day after birth	23	102.0	89
5th day after birth	21	100.5	91
7th day after birth	18	102.0	91
10th and 12th days after birth	10	100.5	88

1. The horizontal chest circumference (at the nipples) is markedly increased at the first inspiration. In the first day, within twelve hours after birth, it enters a period of decrease which continues for two or three days and which is followed by a period of circumference increase. The initial circumference following the first inspiration is regained in the second week.

2. No data are available as to the changes in the circumference of the chest at the tenth rib with the establishment of respiration, although it is probable that they are somewhat similar to those at the nipples,

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14. Champneys, F. H.: Second Communication on Artificial Respiration in Still-Born Children. The Expansibility of the Various Parts of the Lungs, Medico-Chir. Trans., Ser. 2 **42**:87, 1881.

15. These findings are substantially confirmed by G. J. Noback, working in this laboratory, who has investigated the condition of the thoracic viscera of the new-born both in the fresh condition and after intravascular fixation. His results will be published separately.

although less extensive. After respiration is established, the circumference at the tenth rib undergoes, first, a decrease, and then an increase, in a manner similar to that of the circumference at the level of the nipples.

3. The anteroposterior and the transverse diameters of the thorax, both at the level of the nipples and at the level of the tenth rib, show changes comparable with those of the circumferences at these levels. They decline in magnitude from the first to the fifth day after birth, and then enter a period of recovery, the initial dimensions (after respiration is established) being regained about the middle of the second postnatal week. The anteroposterior diameters undergo a much greater reduction than the transverse diameters.

4. The thoracic index at the nipples stands at about 86 before birth. With the establishment of respiration it rises to an average of 106 and then drops to about 102 in the first twenty-four hours. During the remainder of the neonatal period, it declines irregularly and slowly, being 100.5 in the middle of the second week. The changes in the thoracic index at the level of the tenth rib are of the same general character as those at the level of the nipples but are less pronounced.

5. The changes in the form and dimensions of the chest in the neonatal period (with the exception of the postnatal loss in circumference and diameter which seem to be associated with postnatal weight loss) are reflected in the order and degree of expansion of the different parts of the lungs.

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THE EFFECTS OF ACUTE AND CHRONIC INANITION UPON THE DEVELOPMENT AND STRUCTURE OF THE TESTIS IN THE ALBINO RAT

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FOURTEEN FIGURES

CONTENTS

Material and methods.......... 356
Observations.......... 357
  1. Normal postnatal histogenesis of the testis.......... 357
  2. Changes in young rats subjected to acute inanition.......... 362
  3. Changes in rats held at maintenance by underfeeding from three to ten weeks of age.......... 364
  4. Changes in young rats retarded by underfeeding for long periods beginning at three weeks of age.......... 367
  5. Changes in adult rats after acute inanition.......... 369
  6. Changes in rats refed after underfeeding beginning at three weeks of age and extending for various periods.......... 372
Discussion.......... 375
  1. Origin and significance of polynucleated giant cells.......... 375
  2. Mitosis during inanition.......... 375
  3. Interstitial tissue during inanition.......... 376
Summary.......... 377
Bibliography.......... 379

The immediate and the remote effects of inanition upon the young organism are subjects of interest and importance, especially at the present time. Experimental studies in this field have yielded much of importance to biology in general and to medicine in particular. It is very desirable to know more about the changes produced in the sex glands of malnourished or undernourished infants and children, and the resulting effects upon the reproductive system in later adult life. Inanition in adults may also occur either alone or associated with acute or especially with chronic wasting diseases, causing degenerative processes in the sex glands. Recent work on vitamine deficiencies (by McCarrison, Allen, Dutcher, and others) indicates that the changes produced in the sex glands by this partial inanition resemble those found after general inanition. A study of the changes occurring in the histological structure of the testis of the albino rat during experimental inanition at various ages was therefore undertaken, and the results are embodied in the present paper.

MATERIAL AND METHODS

A large part of the material for this investigation was presented to me by Dr. C. M. Jackson, to whom the writer is also very much indebted for constant advice, aid, and criticism throughout the course of this study. The material comprises the testes of several albino rats (Mus norvegicus albinus) that had been subjected to inanition experiments in the Institute of Anatomy. The adult animals during acute inanition were allowed water only; but one of the adults was placed on total inanition, as were also the young rats (two days old) which were removed from the mother and given neither food nor water. Those on chronic inanition were fed restricted amounts of Graham bread soaked in whole milk for various periods. Some were refed fully after underfeeding for various periods. The animals were killed by chloroform and autopsied, the testes being weighed (without epididymis) and portions fixed for histological study. For convenience the material at my disposal is grouped as shown in table 1. In the first column, representing the individual rat numbers, the letters indicate the series (those autopsied by myself are 'Si'), the number following indicates the litter, while the number after the decimal point identifies the individual rat.

The testes had been fixed in either Zenker's, Bouin's, or Flemming's fixatives. Paraffin sections were cut at 2 to 10μ in thickness. The sections were stained chiefly with haematoxylin and eosin, Weigert's iron haematoxylin counterstained with Van Gieson's stain, or Heidenhain's iron-alum haematoxylin counterstained in some instances with orange G or acid fuchsin. In general, Heidenhain's iron-alum haematoxylin without any counterstain gave by far the best results.

My own material was fixed in Carnoy's mixture (no. 1) and in Bouin's fluid. Fixation for one hour with Carnoy's mixture was found to be best. Sections were stained with Heidenhain's iron-alum haematoxylin with or without counterstain (acid fuchsin). This gave clear-cut karyokinetic figures in all stages of mitosis.

A number of measurements of cross-sections of tubules were also taken from the stained sections by means of a micrometer eyepiece. Sections of each testis containing the largest number of tubules cut in cross-section were chosen. In each section all the tubules showing a true cross-section (approximately circular) were measured. The results embodied in table 1 are therefore the average of measurements of a variable number of tubules, ranging from 8 to 44 in the individual cases. While the observations are relatively few in number, they are sufficient to indicate clearly any marked change in size.

In addition, a few (ten to fifteen) nuclei of the interstitial cells in both the control and the test rats were measured at various stages and the averages calculated. Only a sufficient number of testes was taken from each group to determine whether any marked change in the size of the nuclei had taken place as a result of the test conditions. The results are listed in table 1. No measurements of the cell body were attempted, on account of the irregularity of form. Measurements on the seminiferous epithelial cells were likewise found to be impracticable.

OBSERVATIONS

1. *Normal postnatal histogenesis* (*group I*)

In order to understand more fully the changes which inanition produces in the testis, it is essential to review briefly its normal histological structure and histogenesis as a basis for comparison.

Newborn (fig. 1). In microscopic sections of the testis in the newborn rat, the seminiferous tubules appear closely packed together at the periphery of the testis, while in the center of the

TABLE 1

Individual number, age and condition, gross body weight and weight of the testes in the albino rats used for histological study

RAT NUMBER	AGE, ETC.	FINAL BODY WEIGHT	WEIGHT OF TESTES	PER CENT OF BODY WEIGHT	AVERAGE DIAMETER OF TUBULES	AVERAGE DIAMETER OF NUCLEI OF INTERSTITIAL CELLS
Group I—Normal controls						
		grams	*grams*	*per cent*	*micra*	*micra*
Si 1.4	Newborn	5.1	0.0029	0.027	37.2	7.1
Si 2.5	4 days	7.1	0.0061	0.085	42.1	7.1
Si 1.2	4 days	7.0	0.0045	0.064	41.3	
Si 1.3	7 days	9.1	0.0200	0.219	50.5	6.9
Si 1.5	14 days	14.7	0.0780	0.529	65.3	
Si 6.0	21 days	20.6	0.0920	0.446	99.7	4.7
K 8.1	30 days	26.0	0.1154	0.443	88.1	
Si 12.1	35 days	38.7	0.2895	0.748	210.3	
Si 7.1	43 days	36.2	0.3940	1.088	235.0	
St 5.2	56 days	77.0			222.4	
Si 10.1	56 days	48.2	0.5460	1.112	175.7	4.5
Si 11.1	63 days	58.3	1.0030	1.720	204.5	4.6
Si 8.2	70 days	140.0	2.6930	1.923	257.8	
S 14.0	450 days	314.0	2.7545	0.877	323.7	4.5
Group II—Acute inanition in rats starting two days after birth						
Si 1.1	Starved 48 hrs.	4.01 (loss 25%)	0.0043	0.107	34.9	
Si 2.3	Starved 40 hrs.	4.21 (loss 21%)	0.0051	0.121	39.5	
Si 2.6	Starved 50 hrs.	4.10 (loss 25%)	0.0045	0.109	40.7	7.0

Group III—Held at constant body weight by underfeeding from three weeks of age						
St 9.36	Maint. 21–51 days	30.5	0.0958	0.31	100.3	
St 12.71	Maint. 21–67 days	21.2	0.1056	0.50	95.9	4.8
S 7.31	Maint. 21–70 days	31.4	0.3310	1.05	141.8	3.6
S 7.32	Maint. 21–71 days	28.8	0.2100	0.73	102.8	
S 11.65	Maint. 21–73 days	22.5 (R)	0.1860	0.83		
		(L)	0.0496	0.22	75.6	3.7
Group IV—Retarded by underfeeding for long periods beginning at three weeks of age						
St 44.1	Underfed 21–223 days	63.9	1.097	1.72	89.7	4.1
St 44.7	Underfed 21–418 days	40.9	1.187	2.90	91.2	4.4
St 44.4	Underfed 21–428 days	47.0	1.2968	2.75	120.4	4.3
M 29.109	Underfed 70–314 days	68.7	1.099	1.58	196.2	4.4
Group V—Adult acute inanition						
S 25.0	Starved 9 days	198.3 (loss 35%)	1.479	0.75	234.2	4.9
S 26.0	Starved 8 days	171.5 (loss 39%)	1.905	1.11	216.3	4.3
S 27.0	Starved 8 days	219.0 (loss 30%)	2.430	1.11	267.3	
Si 9.1	Starved 11 days	114.0 (loss 47%)	1.468	1.28	168.5	4.2
Group VI—Refed after underfeeding from three weeks to age indicated						
St 12.53	85 days. Refed 3½ days	44.9	0.2010	0.45	98.7	4.2
St 10.26	96 days. Refed 14 days	86.3	0.2672	0.31	123.4	5.3
S 12.52	109 days. Refed 37 days	117.4	1.1848	1.01	223.7	6.5
S 33.118	346 days. Refed 206 days	219.0	2.5182	1.14	291.1	

section the tubules are less compactly arranged. The tubules average 37.2μ in diameter. The intertubular spaces contain many small capillary vessels and mesenchymal cells. The tubules themselves consist chiefly of a single layer of parietal epithelial cells, which apparently correspond to those designated as 'Sertoli cells' by v. Ebner ('02) in the testis of the colt. These cells fuse to form a syncytium. Lumina have not yet appeared in the tubules. The central portion of each tubule contains from one to three large clear cells, each containing a definite, well-marked nucleus. Each nucleus has from one to three small clumps of chromatin situated usually (but not always) close to the periphery of the nucleus. These masses probably represent chromatin nucleoli. These large central cells apparently correspond to those described by v. Ebner ('02, fig. 1147) as the primitive germ cells ('Ursamenzellen') from which the spermatogonia are probably derived.

Interstitial cells (of typical structure) have not yet developed. There is present, however, in the intertubular tissue a peculiar type of cell which appears to be the forerunner of the later interstitial cells (fig. 14, A). This cell contains a large round nucleus (average diameter, 7.1μ) extremely rich in chromatin, which in turn is surrounded by a narrow rim of clear cytoplasm. By the form of its nucleus and its deeply staining chromatin, it is easily distinguished from the ordinary young mesenchymal or connective-tissue cell.

Fourth day (fig. 2). In a normal rat at four days of age the development of the testis has advanced considerably. The whole section is filled with seminiferous tubules (average diameter, 41.7μ). Within the tubules themselves the parietal cells show no material increase in number, but the spermatogonia (Allen's cell type A) have appeared. They are probably derived from the central cells ('Ursamenzellen' of v. Ebner), which still occur (less numerously) and present mitoses, though less frequently than in the newborn. Before dividing, they often appear to migrate from the center of the tubule toward its periphery and crowd in among the parietal cells. Some tubules already contain a few cells which resemble Allen's type B; that is, a primary spermatocyte cell in its earliest phase. The forerunners of the interstitial cells are beginning to group themselves together in the intertubular spaces.

One week (fig. 3). A section of the testis from an albino rat at seven days shows an increase in the number and size of the tubules (average diameter, 50.5μ). (The larger number of tubules appearing in a cross-section of the testis may, however, be due to an increase in the length of the tubules rather than an actual increase in their number.) This represents the earliest stage described by Allen ('18). The tubules now contain two or three layers of cells. Very few central cells still remain, but spermatogonia (Allen's type A) are present in large numbers. There are very few type B cells. In other words, an undifferentiated condition of the spermatic epithelium still prevails. The syncytium (Sertoli syncytium) which fills the tubules at this stage is exceptionally well shown. The number of mitotic figures has again increased, so there are now as many figures in the field as there were at birth. The interstitial cells are more numerous and the amount of interstitial tissue is increased.

Two weeks (fig. 4). There is a large increase in the apparent number of seminiferous tubules, and their average diameter has increased to 65.3μ. There are many cells of types A and B, and some tubules even show Allen's type C (spermatocytes in which the chromatin masses become more diffuse than in type B and assume a 'woolly appearance'). A few cells have advanced as far as the leptotene stage. It is now fairly easy to distinguish between Sertoli cells and spermatogonia. The Sertoli cell has a nucleus with only a little chromatin material, in this way differing from the nucleus of the spermatogonium, which has a large amount of deeply staining chromatin.

Three weeks (fig. 5). Lumina are just beginning to appear in the closely packed tubules, whose average diameter has now increased to 99.7μ. Spermatogonia, cells of types A, B, and C, are numerous. A few tubules already contain primary spermatocytes showing mitotic figures. In many places, degenerating primary spermatocytes and spermatogonia are also present. This appears to be a normal physiological process, occurring in the testis at all ages. No secondary spermatocytes or spermatids are to be seen. The interstitial tissue is assuming its adult structure (fig. 14, *B*). The nuclei average only 4.7μ in diameter, which is much smaller than at birth (7.1μ).

One month (fig. 6). The testis at this stage shows only a slight advance in development. It is distinguished by the large number of primary spermatocytes present. Spermatids have not yet appeared. The interstitial tissue shows no change.

Six to ten weeks. Sections of testes from forty-three to seventy days of age show a gradual increase in the size of the tubules (table 1) and in the number of mature sperm elements. Mature spermatozoa appear for the first time at the age of forty-three days. Their number increases so rapidly that at eight weeks (fig. 7) the histological structure of the testis differs in no important respect from that in the older rats. The interstitial cells show no noticeable change in structure.

Judging from the statements of Hewer ('14) and Allen ('18), there appears to be considerable variation in the age at which the various steps in the process of spermatogenesis occur in the albino rat. Hewer reported that there is no differentiation of primary spermatocytes from spermatogonia until the twenty-fifth day after birth. Allen found that his rats reached the pachytene stage at two weeks; while my material first shows this stage at three weeks. Hewer found that lumina first appear in the tubules at seven weeks. Allen demonstrated them in all rats fourteen days old. In my own rats fourteen days old I found no evidence of definite lumina, but they begin to appear at twenty-one days. Hewer stated that spermatozoa are not present in the lumina of the tubules until nine weeks after birth. Allen found spermatozoa in rats at the age of thirty-seven days, which corresponds closely with my observation at forty-three days.

2. Changes in young rats subjected to acute inanition (Group II)

A comparison of the testes of the normal control (at four days) with those of the test animals of same age (but lesser body weight) in table 1 shows but little apparent retardation in the growth in weight of the gonads of the latter (average weight in two controls, 0.0053 gram; in three test rats, 0.0046 gram). Although the test rats were kept on total inanition for forty-eight to fifty hours, the testes have evidently maintained nearly normal growth, although the body weight has decreased 21 to 25 per cent.

The remarkably persistent growth of the testes in the starved rats is especially evident upon comparison with the newborn of the same litter (Si 1.4). The starved rats have decreased in body weight until they, although four days old, are about 20 per cent below the normal newborn. The testes, however, show a large increase in weight (in spite of the total inanition). The change in weight from 0.0029 to an average of 0.0046 grams represents an increase of 59 per cent. This is in general agreement with the results of Stewart ('18), who found that in rats kept at maintenance (constant body weight) by underfeeding from birth to (average) sixteen days the testis apparently increased about 374 per cent in weight. The smaller increase in the testes of my starved rats is probably due to the greater severity and shorter duration of the inanition.

My measurements indicate that this increase of 59 per cent in the weight of the testes is due almost entirely to the increased number of tubules seen in a section. The size of the tubules has remained about the same. There has perhaps been some retardation of the normal growth in size of the tubules. The normal testis at four days shows an average tubular diameter of 41.7μ, while the average diameter of the tubules in group II is only 38.4μ. This small difference, however, is of doubtful significance.

All three of the starved young rats (Si 1.1, Si 2.3, Si 2.6) show practically the same histological structure in the testis. The tubules are close together and more numerous than in the newborn, although there are relatively few in the center of the section. Cell differentiation has not progressed much beyond that found in the newborn. Each tubule presents the single layer of parietal cells. These cells are all alike and contain large nuclei, with very little chromatin material, surrounded by a narrow strip of clear cytoplasm. The central cells ('Ursamenzellen' of v. Ebner) like those already described in the normal testis are also still present. There are very few mitotic figures either among the parietal cells or the central cells (fig. 8). Sections (stained with iron-alum haematoxylin) of the testes of controls show many mitotic figures in each field (figs. 1 and 2). This decrease in the number of karyokinetic figures is probably due to the condition of inanition. In general, the histological picture shows that the testis has advanced to the stage when type A cells are beginning to appear. Thus the stage of differentiation is somewhat beyond that corresponding to the normal at similar body weight, but behind that corresponding to the age or actual testis weight. The increase in the (apparent) number of tubules evidently accounts for the increase in the size (weight) of the testis.

Swingle ('18) similarly found that total starvation inhibits the growth and metamorphosis of Rana pipiens larvae. Spermatogenesis ceases and sex differentiation is prevented.

3. Changes in rats held at maintenance by underfeeding from three to ten weeks of age (group III)

In the five rats of this group held nearly at constant body weight by underfeeding from three to about ten weeks of age, the testes, though below normal weight for that age, have been retarded in their growth far less than has the body weight. Thus on comparing the average data for group III (table 1) with the normal control at three weeks (Si 6.0) it appears that the body weight has increased from 20.6 grams to 26.9 grams, an increase of about 31 per cent; while the testes have increased from 0.0920 gram to an average of 0.1955 gram, an increase of about 113 per cent. This would indicate a relative growth for the testis even greater than that (+34 per cent) found by Jackson ('15 a) under similar conditions. Individual variations in the control or test rats probably account for the difference.

The size of the tubules in group III has apparently increased from an average diameter of 99.7μ (normal at three weeks of age) to an average diameter of 110μ. This increase in diameter (though of doubtful significance) would indicate that the increase in the weight of the testes is due in part to the increase in the diameter of the tubules.

With the exception of one rat (S 11.65), which will be mentioned later, the testes in this group all present the same microscopic picture (fig. 9). The tubules are placed close together. Lumina are just beginning to appear, although most of the tubules still show no central lumen. No spermatozoa or spermatids are present. There is no evidence to indicate that they had ever been developed and had undergone necrosis. A few secondary spermatocytes can be seen, but they are abnormal in structure.

Almost every primary spermatocyte also shows some degenerative changes. The cytoplasm becomes coarsely granular and contains clumps of basophilic staining material. Other cells show a fatty (?) degeneration or vacuolization of the cytoplasm (a positive statement cannot be made, as material stained for fat was not available). The nuclei degenerating by a process of karyorrhexis may give rise to the basophilic granules present in the cytoplasm of so many spermatocytes. The pycnotic nuclei are very abundant and, with progressive necrobiosis, appear gradually to lose their staining capacity, terminating in karyolysis. The cytoplasm also progressively loses its staining capacity and gradually disappears.

The spermatogonia, however, appear nearly normal. The Sertoli cells are increased in number, but show no structural changes. The tubules are filled with a structure resembling the 'degeneration reticulum' described by Kuntz ('20) in the testis after division of the nerves. This appears to me to be due largely to the Sertoli syncytium which becomes visible in direct ratio to the number of other cells which are being destroyed. Allen ('19) pointed out that in normal tubules the Sertoli syncytium is hard to see on account of the closely packed germ cells. As a result of experimental conditions, the syncytium is made more prominent by the removal of the germ cells which normally obscure it.

There are present in all cases many multinucleated or giant-cells. These cells are situated in the center of the lumen, and each tubule usually presents one or two of them. Each cell may contain from two to four nuclei, all showing some degenerative changes. Multinucleated cells appear to be very characteristic of the degenerative process in the testis. To a certain extent, the degree of severity of the starvation can be measured by the size of these cells and the number of nuclei they contain. For example, absolute inanition for nine days (in the adult) produces giant-cells containing as high as twelve to fifteen nuclei, while in the slower chronic inanition in the present group, the number is reduced to three or four nuclei.

One other important fact, which is strikingly illustrated in these sections, is the remarkable persistence of mitotic figures in the spermatogonia and primary spermatocytes. In rats which have been kept at constant body weight by underfeeding for seven weeks, the number and structure of the mitotic figures is apparently normal as compared with control rats (from three to four weeks). This fact is in agreement with the observations by many investigators (mentioned later) who have reported the presence of mitotic figures after prolonged chronic inanition. This mitosis is doubtless correlated with the persistent growth of the testis in the underfed young rats under these conditions, the new cells formed being in excess of those destroyed by degeneration.

My study of this group of albino rats kept at maintenance by underfeeding from three to ten weeks leads to the following conclusions: First, the chronic inanition prevents the testis from reaching the stage of spermatogenesis normal for the corresponding age. Second, in spite of the persistent mitosis and increased size of the testis, the process of spermatogenesis remains at the stage where spermatocytes are produced, corresponding to the normal stage at the age of three or four weeks. The growth capacity of the testis under these conditions of subnormal nutrition is apparently sufficient only to produce primary spermatocytes from the spermatogonia. Third, the spermatocytes degenerate and are absorbed, though not so rapidly as they are formed.

The excess of production over destruction partly accounts for the continued growth in weight of the testis. Fourth, the interstitial tissue is apparently unchanged and resembles in quantity and structure the tissue present in a normal rat at the age of three or four weeks.

In one rat (S 11.65, fig. 10) in this group, the testis shows such remarkable changes that it seems advisable to describe it separately. This was the left testis (indicated by (L) in table 1), which was markedly atrophic, weighing only 0.0496 gram. All the tubules show degenerative processes. Many contain no cells whatever. The lumina are filled with the characteristic 'degeneration reticulum,' and some have large vacuoles in their centers. Pycnosis, karyorrhexis, and karyolysis are prevalent.

A few of the seminiferous tubules in this case show a type of degeneration which differs entirely from any other thus far described. All the nuclei in every cell in the tubule gradually and almost uniformly lose their basophilic staining capacity and become acidophilic, taking the red counterstains. At the same time the cytoplasm of all the cells fuses together and becomes homogeneous in appearance. So that the entire cytoplasm in the tubules finally becomes one single mass, resembling very closely the homogeneous mass of necrotic tissue seen in an infarct. This mass apparently undergoes a process of autolysis, and vacuoles later replace the cytoplasmic substance. This process continues until finally the structure disintegrates and the position of the tubule is indicated by only the membrana propria. In spite of this necrosis in the tubules, the intertubular tissue shows no marked degenerative changes. However, a very irregularly distributed moderate hyperplasia of the interstitial cells is apparent (fig. 14, *D*). While not the typical picture produced by the chronic inanition in group III, this condition evidently corresponds to the advanced degenerative process in an extreme case.

4. Changes in young rats retarded by underfeeding for long periods beginning at three weeks of age (group IV)

In the three rats underfed from three weeks to 223 to 428 days of age (table 1) the body has approximately doubled in weight, whereas normally it should have increased to about twelve times the initial weight. The testes are likewise of course far below norm for the corresponding age, though apparently considerably above the norm for the younger rats of similar body weight (rats Si 10 and Si 11; also Donaldson's Wistar norm). Stewart ('18), however, concluded that in rats underfed beginning at three weeks of age so as to reach only about 50 grams in body weight at 412 days of age the testes average 42 per cent below normal (for corresponding body weight). It is evident that the changes in the weight of the testis are extremely variable, so it is unsafe to draw general conclusions from only a few cases.

Judging from the size of the tubules in normal testes of similar weight, the tubules in group IV should average above 200μ in diameter. As shown in table 1, however, in three of the four cases the tubules appear subnormal (90 to 120μ) in diameter.

Microscopic sections (stained with haematoxylin and eosin) of the testis show that the size of the tubules in these rats long underfed has considerably decreased. The number of tubules has also decreased and they have become widely separated (fig. 11), due in part to the accumulation of fluid in the interstitial spaces (edematous infiltration). No mature spermatozoa or spermatids appear, although they are present in normal rats of corresponding body or testis weight. Spermatogenesis here (as in group III) has apparently not passed the primary spermatocyte stage. Most of the tubules contain three to four layers of cells, composed of spermatocytes and spermatogonia. The former show the most profound changes. Some appear as shadows without any nucleus or cytoplasm. Others have pycnotic nuclei and a homogeneous cytoplasm. Multinucleated giant-cells are present and the nuclei in these cells show pycnotic changes. Many spermatogonia and all the Sertoli cells appear normal. Mitotic figures are still present. Apparently some vascular changes have taken place. There is a slight sclerosis in the walls of the blood-vessels and also (apparently) a reduced blood-supply to the tubules. There is not any noticeable increase in the quantity of interstitial tissue (proper) (fig. 14, *E*) or any appreciable change in the structure of the interstitial cells, but the quantity of interstitial fluid has enormously increased.

Since all three rats (St 44.1, St 44.4 and St 44.7) show the same histological structure, the question of individual variation may be excluded. So that it appears that the 'growth tendency' so strongly manifested in the testis during inanition in young animals is confined to the formation of the earlier cells in the spermatogenetic cycle; that is, the process can go only to the spermatocyte stage. This is probably what happened in the case of the rats in group III, as before mentioned.

In one rat (M 29.109) inanition was started at ten weeks of age after the testis had presumably reached the stage when mature spermatozoa are produced. Even though kept at maintenance (constant body weight) by extreme underfeeding for 244 days, this testis shows the following histological structure. Most of the tubules are normal in structure and size and show well-developed spermatozoa. However, many lumina are filled with a débris made up almost entirely of heads and tails of spermatozoa. A few tubules show a slight desquamation process, but this is not distributed evenly among the tubules and is probably of no importance. Aside from this, the structure of the testis is apparently normal. Mitotic figures are present and all the various stages of spermatogenesis can be followed out. The conditions in this case emphasize the importance of the age factor. It indicates that if the testis has reached sexual maturity before experimental inanition, the effect upon spermatogenesis is much less marked than in cases where the underfeeding is begun at an earlier period, although the further growth of the testis (in weight) may be hindered. No final conclusions can be drawn from this one rat, however, although the results are in agreement with the conclusions of Jackson and Stewart ('20) as to the importance of the age at which the inanition begins.

5. Changes in adult rats after acute inanition (group V)

As shown in table 1 (group V), adult rats were subjected to acute inanition for periods varying from nine to twelve days. The loss in body weight varies from 30 to 47 per cent. The testes also apparently lose a great deal in weight, but the exact amount can of course be only roughly estimated. The test rats at the beginning of the experiment varied in body weight from 216 to 328 grams. According to the Wistar norm tables compiled by Donaldson ('15), these body weights call for from 2.5 to 2.8 grams of testis. A comparison with the figures in table 1 shows that at autopsy the testes in weight varied from 1.468 to 2.43 grams, indicating considerable loss in weight. The average diameter of the tubules has correspondingly decreased from over 300μ to an average of 221.5μ. Jackson ('15) found that the loss in weight of the testis of adult rats during acute inanition is nearly proportional to that of the whole body. This agrees in general with the results obtained by Falck ('54), Voit ('66), Manassein ('68), and Gerhartz ('09). An atrophy of the testis relatively much greater than the decrease in body weight during inanition was noted in birds by Grandis ('89), and (during vitamine deficiency) by McCarrison ('19) and Dutcher ('20). A similar result in rats on lipoid-free diet was noted by Hatai ('15).

In one rat (Si 9) which was held for eleven days without food or water, the testis had shrunken away from the tunica albuginea and had decreased considerably in size. This was, however, not apparent upon removing the organ at autopsy, because the intervening space was filled with a fluid, which kept the tunic distended and gave it a normal rounded appearance. This phenomenon has likewise been noted by Allen ('19) in his study of rats subjected to a diet deficient in the water-soluble vitamines.

At first glance, the sections of the testes in this group appear perfectly normal in structure. The majority of the tubules are apparently normal in shape and show no signs of degeneration, as was likewise noted by Simonowitsch ('96). Spermatogenesis appears to be going on as usual. Spermatozoa are abundant and show no alteration in structure. There is no apparent change in the amount or structure of the interstitial tissue.

However, more careful study shows that in each section a few tubules have suffered as a result of the inanition. These tubules, though few in number and placed in immediate relationship with perfectly normal tubules, may show very marked and very severe changes (fig. 12). The spermatozoa are irregular in structure and show extreme degenerative processes. The spermatids may present a picture which strongly suggests a true synizesis. This peculiar clumping of the chromatin toward the periphery and toward one side of the nucleus has been described by Monterosso ('12) as a form of degeneration. But I have observed this same structure in almost everyone of my control rats, and believe that we are dealing here rather with a rearrangement of the chromatin material in the normal cytomorphosis of the cell.

The secondary and primary spermatocytes show marked necrobiotic changes. Even the spermatogonia are involved and reveal pycnotic and karyolytic changes in the nuclei. The Sertoli cells are apparently the only ones not severely injured.

Depending on the stage of degeneration, large numbers of multinucleated giant-cells are present in the tubules. These cells each contain from four or five nuclei up to as many as twelve or fifteen nuclei. Some tubules are so atrophic and degenerated that only the membrana propria remains, with a few necrotic giant-cells in the lumina. These giant-cells were carefully studied with special reference to their origin. Apparently they are derived from primary spermatocytes, which fuse together in groups during their desquamation. These cells will be referred to again at a later period.

Desquamation of the epithelial cells in these degenerating tubules is very common and apparently initiates the process of degeneration. This process appears to start with the secondary spermatocytes, but as the sloughing process continues the primary spermatocytes and even the spermatogonia are detached into the degenerating mass in the lumen of the tubule. Degeneration takes place in every case after desquamation has occurred. This degeneration apparently is also always in inverse order to that of spermatogenesis. The spermatozoa are the first to disappear, then the spermatids, followed by the spermatocytes and spermatogonia. The Sertoli cells are the most resistant. This agrees with the results obtained by Monterosso (in starved rats), Bouin and Garnier (in alcoholized rats), and Regaud and Tournade (after ligation of the spermatic cord). Allen ('19) states that (in degeneration due to vitamine deficiency) "the spermatocytes seem to be the first affected, the spermatids next, and the spermatogonia last."

It therefore appears that acute inanition notably affects but comparatively few tubules in the testis, and that the other tubules retain their normal structure, but all the tubules suffer a loss in size. In spite of a loss of about one-third in the weight of the testis, spermatogenesis apparently continues normally in most of the tubules. But the few tubules which for some unexplainable reason are less resistant show atrophic and necrotic changes which are as marked as any found in chronic inanition.

Likewise, atrophic and degenerative changes in the seminiferous epithelium during inanition have been described by Grandis ('89) in pigeons, Pernice and Scagliosi ('95) in chickens, Simonowitsch ('96) in rabbits and guinea-pigs, Loisel ('01) in the dog, Monterosso ('12) in rat and mouse, and Poiarkoff ('13) in the dog. Similar changes have been described as a result of vitamine deficiency by McCarrison ('19) in pigeons and Allen ('19) in rats.

The extent of the degenerative changes naturally varies in general with the severity of the inanition. In the adult rabbit, Traina ('04) found that spermatogenesis ceases when the loss in body weight reaches about 30 per cent.

There is also a variation according to species, season, etc. At certain periods the testis during inanition may even continue to develop at the expense of the remainder of the body in the salmon (Miescher, '97) and frog (Nussbaum, '06).

6. *Changes in rats refed after underfeeding beginning at three weeks of age and extending for various periods (group VI)*

In one rat (St 12.53) refed for three and one-half days (table 1), the refeeding period was too short to produce any definite results. There is apparently already some increase in the total body weight, but very little, if any, in the testis. Sections show no definite change from the appearance of the testes in group IV. The primary spermatocytes still show necrotic changes and there is no advance in the stage of spermatogenesis. The average diameter of the tubules (98.7μ) is slightly below that in rat S 7.32, with similar testis weight.

In another rat (St 10.26), refed for fourteen days after maintenance by underfeeding from twenty-one to seventy-two days, many improvements have taken place. The body weight has increased from around 30 to 86.3 grams, but there is no great increase in the weight of the testes. The reason for this becomes more evident upon histological study. Sections (stained with iron haematoxylin) show no increase in the number and but slight increase in the diameter of the tubules, compared with those of group III. But all the débris has been removed and no degenerating cells are to be seen (fig. 13). No secondary spermatocytes are present. The interstitial cells and their nuclei appear normal (but increased in size). They are, however, definitely increased in number above normal. They are evenly distributed throughout the testis, in this way differing from the condition found by Allen ('19) in the rats of Osborne and Mendel subjected to a diet deficient in the water-soluble vitamines. There are numerous mitotic figures among the spermatocytes and spermatogonia, showing all the stages of the karyokinetic cycle. The blood-vessels are distended with blood. It would appear that all the energy in the testis has been utilized to 'clean up' the waste material and to prepare for a further advance. This may account to some extent for the lack of increase in the weight of the testis.

In the rat (S 12.52) which was refed for thirty-seven days, the weight of the testis has greatly increased and histological study shows that spermatogenesis is going on normally. The tubules are normal in structure and contain many mature spermatozoa. The average diameter of the tubules has, however, increased to 222.7μ, accounting for the increase in weight. The only difference to be found (as compared with normal control testes) is an increase in the amount of interstitial tissue (fig. 14, *F*).

We must distinguish between interstitial tissue and interstitial cells. The former term applies to all tissues outside of the tubules proper; the latter (interstitial cells) refers only to the specific cells playing a part in the internal secretion of the testes. In reality, there is not so much a general hypertrophy of the interstitial tissue, but rather a hyperplasia of the interstitial cells proper. There is a marked increase in the number of these cells and a slight increase in their size. They assume a more or less cord-like arrangement. The nuclei of the cells are spherical and rather vesicular, although a few clumps of chromatin are always present close to the periphery. A light granular cytoplasm surrounds the nuclei. After the very young stages (one to seven days), mitosis among these cells has never been observed. One possible explanation which may be offered is that mitosis in these cells takes place very rapidly, so that, although cell division occurs, it is rarely found in the sections.

The fourth rat in this group (S 33.118), refed for 206 days, has completely recovered from the effects of the underfeeding and presents a perfectly normal adult histological structure. The diameter of the tubules shows an increase of 291.1μ. Even the interstitial tissue and cells appear normal in quantity and structure.

These results are in accord with the work of Stewart ('15), who found that in rats refed after underfeeding from three to twelve weeks of age, the testes remain somewhat below normal weight for a few weeks, but regain normal weight before the adult stage is reached. In later experiments (Stewart, '18), in which the underfeeding was prolonged, the testis became markedly subnormal in weight (as found by Jackson, '15 a). Jackson and Stewart ('19) reported that the testis, which increases in relative weight in young rats during underfeeding, remains somewhat above normal weight during refeeding to a body weight 25 to 50 grams, but is subnormal in those refed to 75 grams body weight. Finally, Jackson and Stewart ('20) found that when the underfed rats are fully refed to maximum body weight, the testes are definitely above normal for the corresponding body weight. A restoration of the testis to normal structure and function upon refeeding after inanition has likewise been noted by Simonowitsch ('96) in rabbits and guinea-pigs, and by Loisel ('01) and Poiarkoff ('13) in dogs.

DISCUSSION

1. Origin and significance of polynucleated giant cells

It has been claimed by some authors that giant-cells may occur normally in the testis. I have never seen either a polynucleated or a giant-cell in a normal seminiferous tubule. Monterosso ('12) found that these cells are very rare in normal tubules, but occur more frequently during early inanition. He found that their number increases with the length of inanition, and that as many as fifteen nuclei might be seen in a single cell. He believes that they are formed by a fusion of the neighboring cells.

On the other hand, Bouin and Garnier ('00) believe that these cells are formed by an abnormal mitosis of the nuclei within the cell. Allen ('19) noticed these cells during the early stages of degeneration, but offered no explanation as to their origin.

My studies lead me to believe that the multinucleated cell is formed by a fusion of primary spermatocyte cells when they begin to degenerate. As a rule, these cells show marked nuclear and cytoplasmic degenerative changes later than those cells which break off independently and do not fuse with other cells. This suggests that fusion of cells may be a sort of protective measure from the effects of the inanition. De Bruyne ('99), however, claims that these polynuclear cells are precursors of degeneration. No mitotic figures have ever been observed in any polynucleated giant-cell.

2. Mitosis during inanition

As to the occurrence of mitosis during inanition, my own observations agree in general with those of Morpurgo ('88, '89), Grandis ('89), Traina ('04), and others. Traina, for instance, found that mitotic figures persist after a loss in body weight of 30 to 35 per cent. On the other hand, Pernice and Scagliosi ('95), in young chickens on water inanition, and Morgulis, Howe, and Hawk ('15), in fasting dogs, reported an absence of mitosis in the testis. In my adult rats subjected to acute inanition

(S 25, S 26, S 27), with loss in body weight of 30, 35, and 39 per cent, mitotic figures are still present in large numbers. Another rat (Si 9), with loss in body weight of 47 per cent, still shows numerous mitotic figures. They are present even in tubules showing extreme degenerative changes. In young rats underfed from the age three to ten weeks, mitosis is apparently unaffected. Even in those animals in which the underfeeding was continued to 400 days or more, the mitotic figures can be seen in many of the tubules. It would therefore appear justifiable to conclude that it is impossible by inanition to suppress mitosis entirely in the epithelium of the seminiferous tubule. The mitoses, however, may be decreased in number, as found in the rats two days old subjected to acute inanition.

The presence or absence of amitosis in the testis has long been a disputed question. Monterosso ('12) found amitosis present among degenerating spermatocytes and spermatogonia. Allen ('18, '19) believes that amitosis does not occur. I have likewise never seen a definite case of amitosis in any of my sections.

3. *Interstitial tissue during inanition*

Some investigators mention the increased quantity of interstitial tissue, which is occasioned by any degeneration or atrophy of the seminiferous epithelium. Cordes ('98) found an increase in interstitial tissue in cases of chronic disease with cachexia. Kyrle ('10) and Voss ('13) pointed out that in diseased conditions and in underdeveloped testes, the tubules are far apart and the interstitial tissue surpasses the tubules in amount. Allen ('19) also found an increase in the quantity of interstitial tissue in rats fed upon a diet deficient in water-soluble vitamines.

In my own series of albino rats, there appears in no case any demonstrable increase in interstitial tissue during either acute or chronic inanition. However, in those rats which were refed after various periods of underfeeding (group VI), there is a gradual increase in the relative amount of interstitial tissue (interstitial cells) until the gland regains its normal size and structure. Thereafter, the interstitial tissue apparently decreases in amount until it reaches the normal proportion. That is, the interstitial cells appear relatively increased in number only during the regenerative period.

Measurements of the nuclei of interstitial cells indicate that there is a sharp decrease in the average diameter of the nucleus from 7.1μ at birth to 4.7μ at three weeks of age. From the three-weeks stage there is very little change in the size of the nucleus. Comparison with the test groups indicates that the size of the nucleus of the interstitial cells is not affected to any marked degree by the inanition tests. In group III, two of the three specimens measured show a decreased average diameter of the nucleus (in underfeeding from five to ten weeks of age); and in group VI, it would appear that refeeding causes some increase in the size of the nucleus, in addition to the numerical increase already noted. There is considerable individual variation, however, and the number of observations is insufficient to warrant final conclusions.

SUMMARY

The results of the present investigation may be summarized as follows:

1. In the normal testis of the albino rat during the first postnatal week the (solid) seminiferous tubules consist of a single layer of parietal cells ('Sertoli cells' of v. Ebner) and a few central cells ('Ursamenzellen' of v. Ebner). After the first week, the normal postnatal development of the testis and the process of spermatogenesis proceed essentially as described by Allen ('18).
2. In rats two days old starved for forty-eight to fifty hours, the testis increases markedly in weight, but mitoses are reduced in number and the normal process of histological differentiation is arrested. The seminiferous tubules remain nearly normal in diameter.
3. During underfeeding for various periods beginning in rats three weeks old, mitosis continues in the cells of the seminiferous tubules, but the process of spermatogenesis is arrested at the primary spermatocyte stage, which persists even in rats over

400 days old. The spermatocytes degenerate and are resorbed, but if the number formed exceeds those destroyed, the testis may increase in weight. Multinucleated giant-cells are formed during the process of degeneration. The spermatogonia and Sertoli cells usually persist unaffected, except in very extreme cases, where a complete degeneration and disintegration of the seminiferous epithelium may occur. If the underfeeding begins after sexual maturity, the seminiferous tissue is much more resistant and normal spermatogenesis may persist for a long time. The seminiferous tubules may increase slightly in diameter in the shorter tests, but usually appear subnormal in size in the longer experiments.

4. Acute inanition in adult rats, with 30 to 47 per cent loss in body weight, produces degenerative changes in a few, irregularly scattered, tubules. All the other tubules show apparently normal structure and spermatogenesis, although there is a general decrease in their size. The degenerative changes are initiated by a desquamation of the epithelial cells into the lumen of the seminiferous tubule, followed by pycnosis and karyolysis. The process involves first the spermatids and spermatozoa, then the secondary and primary spermatocytes, and finally the spermatogonia. The Sertoli cells are the most resistant. During the degenerative process, multinucleated giant-cells arise, apparently by fusion of the degenerating spermatocytes.

5. During inanition, mitosis is very persistent in the seminiferous epithelium, both in young and adult rats. It may occur even in tubules where nearly all the cells are more or less degenerated. Amitosis was not observed. A condition resembling synizesis was frequently observed in the spermatids in both controls and test rats.

6. Refeeding after prolonged inanition (beginning in rats at three weeks of age and extending to twelve to twenty weeks) results in a rapid improvement in the structure of the testis, although it may lag behind in weight for a while during the preliminary stages of reconstruction. Spermatogenesis returns to normal in a short time, the tubules gradually increase to normal diameter, and spermatozoa appeared in thirty-seven days.

7. There is a definite hypertrophy of the interstitial tissue and an increase in the number of interstitial cells of the testis during the regenerative period on refeeding after inanition (in growing rats). No hypertrophy of the interstitial tissue was found accompanying atrophy of the seminiferous epithelium during inanition in either young or adult rats. The structure of the interstitial tissue and the size of the nuclei apparently remain nearly normal during acute and chronic inanition, except in extreme cases, where degenerative changes in the cells may occur.

BIBLIOGRAPHY

ALLEN, EZRA 1918 Studies on cell division in the albino rat (Mus norvegicus albinus). III. Spermatogenesis: The origin of the first spermatocytes and the organization of the chromosomes, including the accessory. Jour. Morph., vol. 31, pp. 133–186.

1919 Degeneration in the albino rat testis due to a diet deficient in the water-soluble vitamine, with a comparison of similar degeneration in rats differently treated and a consideration of the Sertoli tissue. Anat. Rec., vol. 16, pp. 93–117.

BOUIN ET GARNIER 1900 Altérations du tube séminifère au cours de l'alcoolisme expérimental chez le rat blanc. C. R. Soc. Biol. (Cited by Monterosso, '12.)

CORDES, H. 1898 Untersuchungen über den Einfluss acuter und chronischer Allgemeinerkrankungen auf die Testikel, speciell auf die Spermatogenese, sowie Beobachtungen über das Auftreten von Fett in den Hoden. Virchow's Arch., Bd. 151.

DE BRUYNE 1899 Signif. physiol. de l'amitose. C. R. Ass. Anat. 1re session. (Cited by Monterosso, '12.)

DONALDSON, H. H. 1915 The rat. Reference tables and data for the albino rat and the Norway rat. Memoirs of The Wistar Institute of Anatomy and Biology, no. 6.

DUTCHER, R. ADAMS 1920 The nature and function of the antineuritic vitamine. Proc. Nat. Acad. Sci., vol. 6, pp. 10–14.

v. EBNER, V. 1902 In Kölliker's Handbuch der Gewebelehre, 3. Bd., 2. Hälfte, S. 415–416.

FALCK, C. P. 1854 Beiträge zur Kenntnis der Wachsthumsgeschichte des Thierkörpers. Virchow's Arch, Bd. 7, S. 37.

GERHARTZ, H. 1909 Geschlectsorgane und Hunger. 2. Mitteil. Centralbl. f. Physiol., Bd. 22, S. 65–66.

GRANDIS, V. 1889 La spermatogenèse durant l'inanition. Arch. ital. de Biol., T. 12, pp. 680–682.

HATAI, S. 1915 Growth of the body and organs in albino rats fed with a lipoid-free ration. Anat. Rec., vol. 9, pp. 1–20.

JACKSON, C. M. 1915 Effects of acute and chronic inanition on the relative weights of the various organs and systems of adult albino rats. Am. Jour. Anat., vol. 18, pp. 75–116.

1915 a Changes in the relative weights of the various parts, systems and organs of young albino rats held at constant body weight by underfeeding for various periods. Jour. Exp. Zoöl., vol. 19, pp. 99–156.

JACKSON, C. M., AND STEWART, C. A. 1918 The effects of underfeeding and refeeding upon the growth of the various systems and organs of the body. Minnesota Medicine, vol. 1, pp. 403–414.

1919 On the recovery of normal weight in the various organs of albino rats upon refeeding after underfeeding from birth for various periods. Amer. Jour. Diseases of Children, vol. 17, pp. 329–352.

1920 The effects of inanition in the young upon the ultimate size of the body and of the various organs in the albino rat. Jour. Exp. Zoöl., vol. 30, pp. 97–128.

KUNTZ, ALBERT 1919 Degeneration of testis in the dog. Anat. Rec., vol. 17.

KYRLE, J. 1910 Ueber Entwicklungsstörungen der männlichen Keimdrüsen im Jugendalter. Wiener klin. Woch., Bd. 23.

LOISEL, GUSTAVE 1901 Influence du jeûne sur la spermatogénèse. C. R. Soc. d. Biol., T. 53, p. 836.

MANASSEIN, W. 1868 Zur Lehre von der Inanition. Centralbl. f. d. med. Wissensch. (Berlin), Bd. 6, pp. 273–275.

McCARRISON, R. 1919 The pathogenesis of deficiency disease. Indian Jour. Med. Research, vol. 6, no. 3, pp. 275–355. (Also in Brit. Med. Jour., 1919, vol. 1, p. 177, and vol. 2, no. 3033.) (Abstracted in Jour. Am. Med. Ass., vol. 74, no. 12.)

MIESCHER, FR. 1897 Histochemische und physiologische Arbeiten, Leipzig, Bd. 2, S. 116–217.

MONTEROSSO, BRUNO 1912 L'azione del diguino e dell'estratto secco di tiroide sulla struttura dell'epitelio del tubo seminifero del topo. Archiv. de Biol., T. 27, pp. 35–62.

MORGULIS, S., HOWE, PAUL E., AND HAWK, P. B. 1915 Studies on tissues of fasting animals. Biol. Bull., vol. 28, pp. 397–406.

MORPURGO, B. 1888 Sul processo fisiologico di neuformazione cellulare durante la inanizione acuta dell'organismo. Arch. per le sc. med., T. 12, pp 395–418. (Also in Arch. ital. de Biol., 1888, T. 11, pp. 118–133.)

1889 Ueber den physiologischen Zellneubildungsprocess während der acuten Inanition des Organismus. Ziegler's Beiträge zur path. Anat. u. allg. Path., Bd. 4, S. 315–335.

NUSSBAUM, E. 1906 Fortgesetzte Untersuchungen über den Einfluss des Hungers auf die Entwicklung der männlichen Geschlechtsorgane der Rana fusca. Anat. Anz., Bd. 29, S. 315–316.

PERNICE UND SCAGLIOSI 1895 Ueber die Wirkung der Wasserentziehung auf Thiere. Virchow's Arch., Bd. 139, S. 155–184.

POÏARKOV, E. 1913 L'influence de jeûne sur le travail des glandes sexuelles du chien. (Communication préliminaire.) C. R. Soc. Biol. Paris, T. 74, pp. 141–143.

REGAUD ET TOURNADE 1903 Notes hist. sur les phénom. régressifs détermines dans le test. par l'oblitération du canal déférent. C. R. Soc. de Biol. (Cited by Monterosso, '12.)

SIMONOWITSCH, J. 1896 Ueber pathologisch-anatomische Veränderungen der Hoden bei vollständigem und unvollständigem Hungern der Thier und Auflütterung nach dem Hungern. (Cited by Mühlmann—Russiche Literatur über die Pathologie des Hungerns. Centralbl. f. allg. Path. u. Path. Anat., Bd. 10, S. 160.)

STEWART, C. A. 1916 Growth of the body and of the various organs of young albino rats after inanition for various periods. Biol. Bull., vol. 31, pp. 16–51.

1918 Changes in the relative weight of the various parts, systems, and organs of young albino rats underfed for various periods. Jour. Exp. Zoöl., vol. 25, pp. 301–353.

SWINGLE, W. W. 1918 The effect of inanition upon the development of the germ glands and germ cells of frog larvae. Jour. Exp. Zoöl., vol. 24, pp. 545–565.

TRAINA, R. 1904 Ueber das Verhalten des Fettes und der Zellgranula bei chronischem Marasmus und akuten Hungerszuständen. Ziegler's Beiträge zur path. Anat. u. allg. Path., Bd. 35, S. 1–93.

VOIT, CARL 1866 Ueber die Verschiedenheiten der Eiweisszersetzung beim Hungern. Zeitschr. f. Biol., Bd. 2, S. 308–365.

VOSS, H. 1913 Zur Frage der Entwicklungsstörungen des kindlichen Hodens. Centralbl. f. allg. Path., etc., Bd. 24, No. 10, S. 433.

FIGURES AND EXPLANATION

The drawings were made with the aid of a camera lucida. The unit of magnification is 630 diameters for all the figures, with the single exception of figure 10, which has a magnification of 127 diameters. All the material stained with Heidenhain's iron-alum haematoxylin had been fixed in Carnoy's fluid (no. 1). The remaining material had been fixed in either Bouin's or Zenker's fixatives.

PLATE 1

EXPLANATION OF FIGURES

Figures 1 to 7 show normal development in the epithelial wall and the growth of the tubules in albino rats from birth to eight weeks of age. All × 630.

Figures 8 to 13 show changes in the seminiferous epithelium and size of the tubules brought about by experimental conditions.

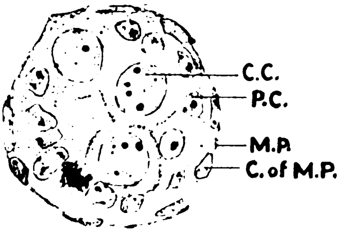
1 Transverse section of a tubule from the testis of a normal newborn rat (Si 1.4). Section 6μ thick; stained with iron-alum-haematoxylin and acid fuchsin. × 630. Note the presence of a single layer of parietal cells, *P.C.*, and the large central cells, *C.C.*, in the center of the tubule Each tubule is surrounded by a membrana propria, *M.P.*

2 Transverse sections of a tubule from the normal testis at four days (Si 2.5). Section 6μ thick; stained with iron-alum-haematoxylin. × 630. The number of parietal cells, *P.C.*, has increased, while the central cells, *C.C.*, are less frequent. Membrana propria, *M.P.*

3 Transverse section of a tubule from the normal testis at seven days (Si 1.3). Section 6μ thick; stained with iron-alum-haematoxylin. × 630. Mitotic activity is apparent. A spermatogonium in metaphase is well shown, *Sp.C.* Germinative cells are all alike (Allen's type A). Membrana propria, *M.P.*

4 Section of a tubule from the normal testis at fourteen days (Si 1.5). Section 6μ thick; stained with iron-alum-haematoxylin and acid fuchsin. × 630. Cells of (Allen's) types A and B are abundant and a few cells of type C are present, *A.*, *B.*, *C.* Sertoli cells, *S.C.*, are beginning to assume their adult position and structure. Membrana propria, *M.P.*

5 Section of a tubule from a normal testis of twenty-one days (Si 6.0). Section 10μ thick; stained with iron-alum-haematoxylin. × 630. All types of cells, *A.*, *B.*, and *C.*, are present. Primary spermatocytes, *P.S.*, have appeared. Sertoli cells, *S.C.* Membrana propria, *M.P.* Note the formation of a lumen, *L.*, in the tubule.



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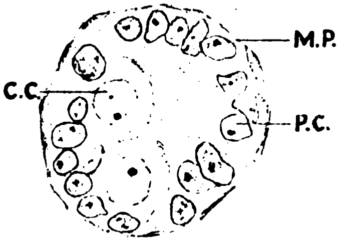

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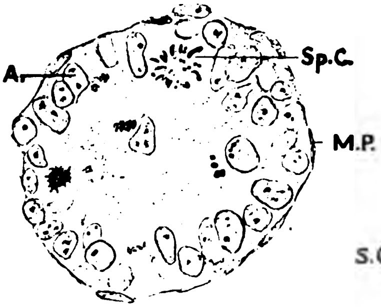

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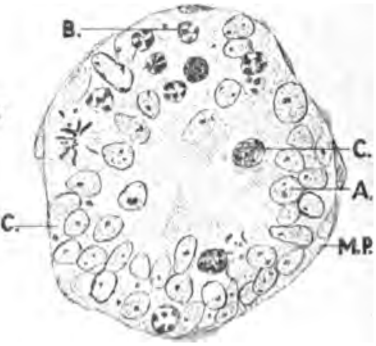

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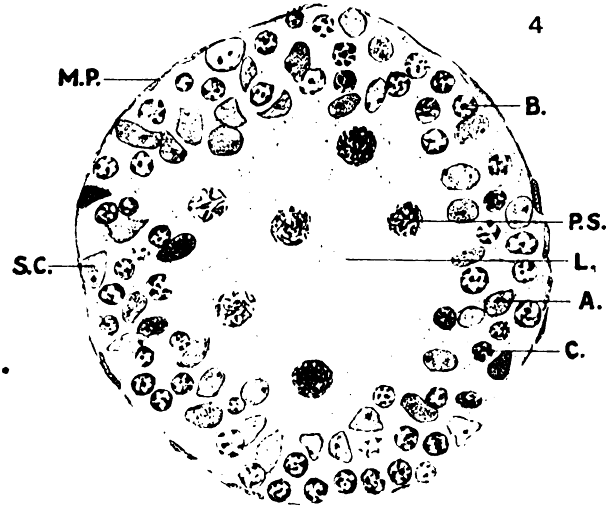

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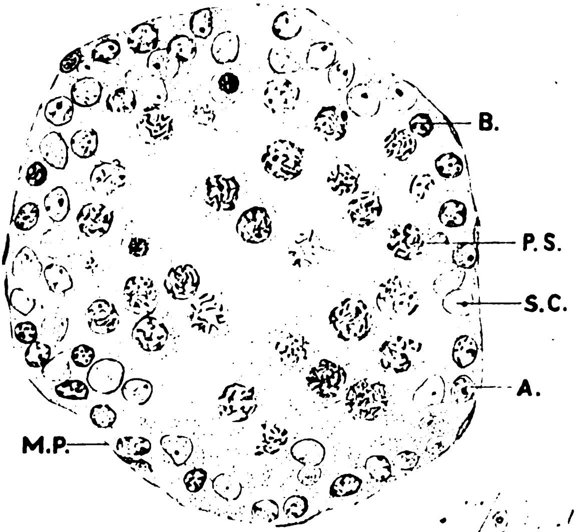
PLATE 2

EXPLANATION OF FIGURES

6 Section of a tubule from a normal testis at four weeks (K 8.1). Section 10μ thick; stained with iron-alum-haematoxylin. × 630. Presents the same picture as the preceding figure, but also shows a marked increase in the number of primary spermatocytes, *P.S.*

7 Portion of a transverse section of a tubule from a normal testis at eight weeks (St 5.2). Section 10μ thick; stained with iron-haematoxylin. × 630. Note the gradual transition from the spermatogonia to the mature spermatozoa. This corresponds very closely to the condition found in the adult testis. Sertoli cell, *S.C.*; spermatogonia, *S.*; primary spermatocytes, *P.S.*; secondary spermatocytes, *S.S.*; spermatids, *Spt.*; spermatozoa, *Sp.*; membrana propria, *M.P.*

8 Section of three tubules from the testis of a rat four days old (Si 2.6) which had been subjected to acute inanition for fifty hours. Section 6μ thick; stained with iron-alum-haematoxylin and acid fuchsin. × 630. Note that the structure resembles that of the newborn more closely than that normal at four days. Compare with figures 1 and 2. Central cells, *C.C.*; parietal cells, *P.C.*; membrana propria, *M.P.*



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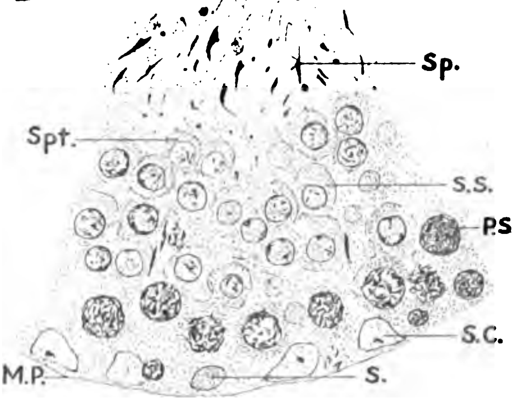

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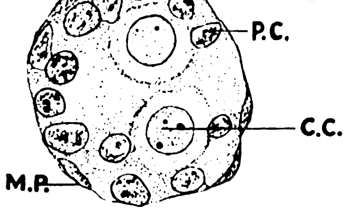

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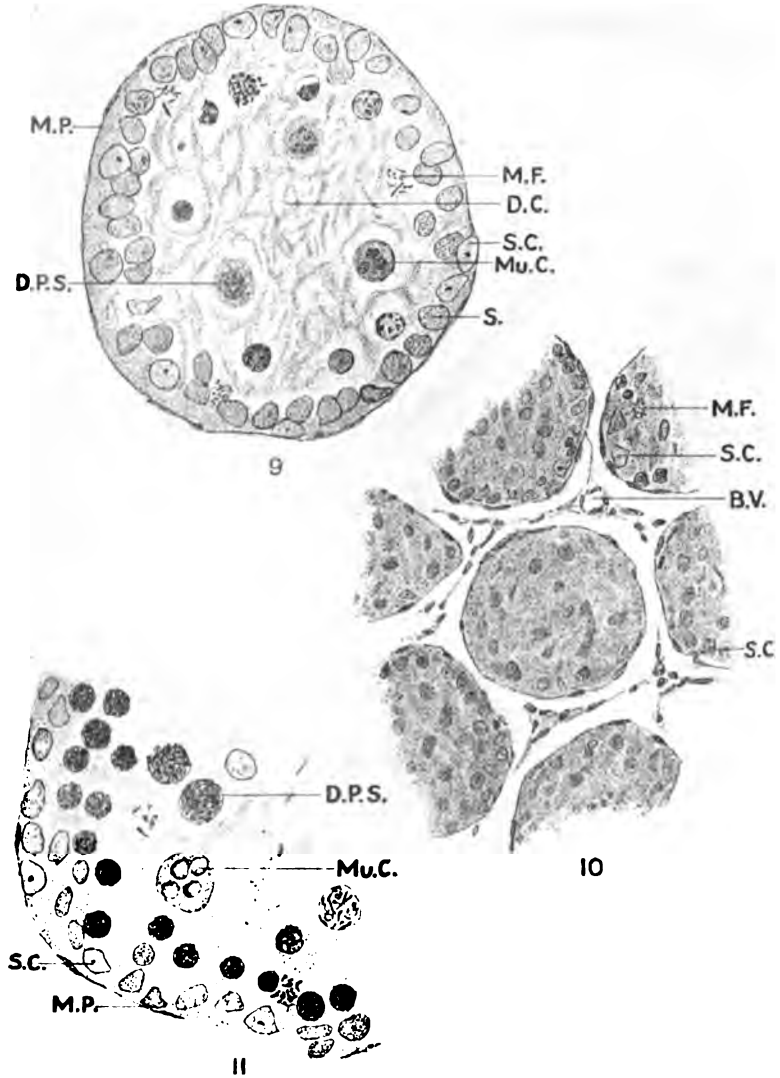
PLATE 3

EXPLANATION OF FIGURES

9 Section of a tubule from a rat (S 7.32) held at constant body weight by underfeeding from three to ten weeks of age. Section 6μ thick; stained with haematoxylin and eosin. × 630. Degenerating primary spermatocytes, *D.P.S.*, showing the homogeneous, deeply acidophilic staining reaction of the cytoplasm. Note the persistence of mitotic figures, *M.F.*; the normal Sertoli cells, *S.C.*, and spermatogonia, *S.* A multinucleated cell, *Mu.C.*, typical of those appearing as a result of chronic inanition. Degenerating cytoplasm, *D.C.*; membrana propria, *M.P.*

10 Section of a portion of the atrophic testis from a rat (S 11.65) subjected to chronic inanition from three to ten weeks of age. Section 10μ thick; stained with haematoxylin and eosin. × 127. The central tubule shows the extreme stage of degeneration (described in text), a complete nearly homogeneous mass of necrotic tissue. The surrounding tubules show various stages of degeneration. Note the mitotic figures, *M.F.*, in the tubule to the right and the apparently normal Sertoli cells, *S.C.* A slight hyperplasia of the interstitial cells, *I.C.*, appears. Blood-vessel, *B.V.*

11 Portion of a tubule from the testis of a rat (St 44.4) stunted by underfeeding from three weeks to 428 days of age. Section 10μ thick; stained with haematoxylin and eosin. × 630. Note the degenerating primary spermatocytes, *D.P.S.*; the multinucleated cell, *Mu.C.*, in the lumen. Sertoli cells, *S.C.*, and spermatogonia, *S.*, are apparently normal. Membrana propria, *M.P.*


M.P.
M.F.
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D.P.S.
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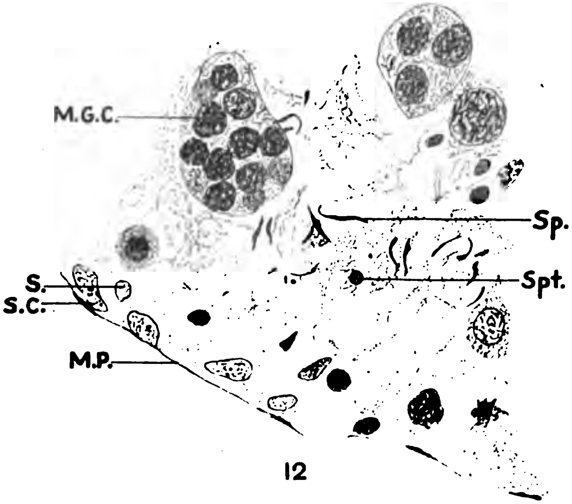
M.P.
11

PLATE 4

EXPLANATION OF FIGURES

12 Oblique section of a testis from an adult rat (S 25) subjected to acute inanition for nine days. Section 10μ thick; stained with haematoxylin and eosin. × 630. Multinucleated giant-cells, *M.G.C.*, occupy the center of the tubule. Débris composed of degenerating cells of various kinds fills the tubule. Spermatozoa, *Sp.*; spermatids, *Spt.*; spermatogonia, *S.*; membrana propria, *M.P.* The Sertoli cells, *S.C.*, still occupy their normal position, but show atrophic and degenerative changes.

13 Portion of transverse section of the testis from a rat (S 12.52) underfed from three to ten weeks of age and then refed for thirty-seven days. Section 7μ thick; stained with haematoxylin and eosin. × 630. Note the large number of normal primary spermatocytes, *P.S.*, and spermatozoa, *Sp.* Spermatogonia, *S.*, showing mitotic figures, are abundant. Sertoli cell, *S.C.*; membrana propria, *M.P.*



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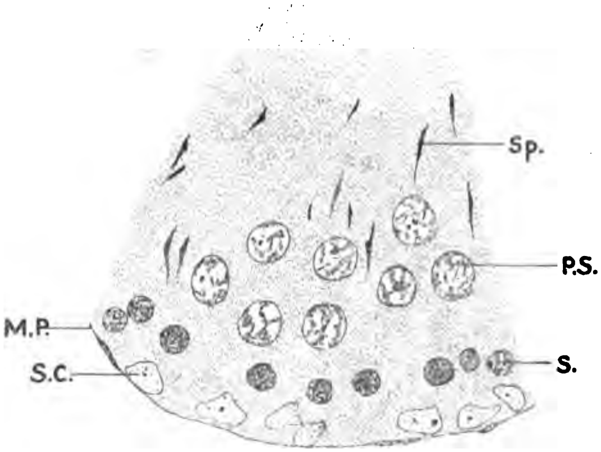

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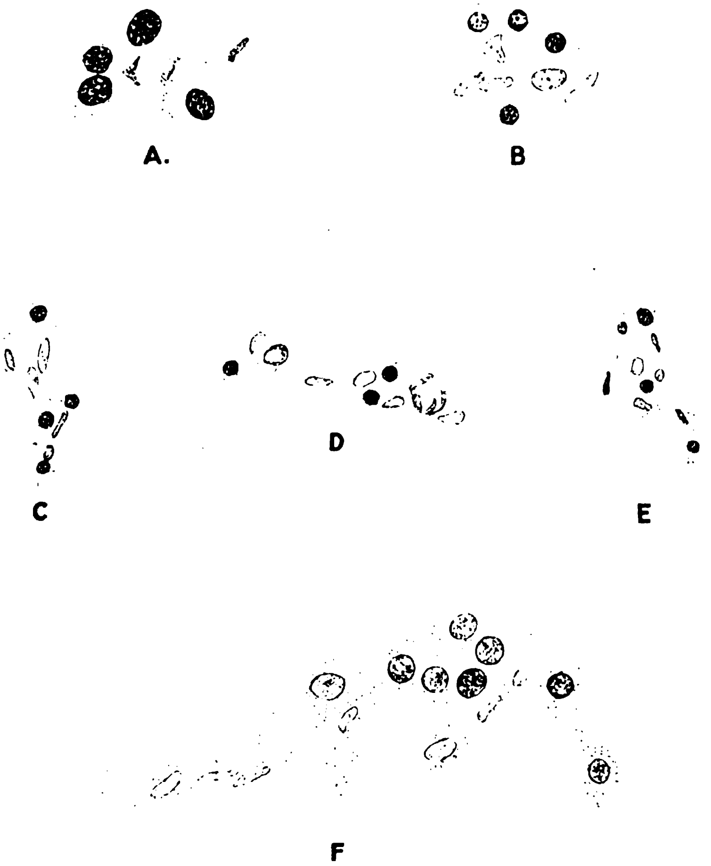
PLATE 5

EXPLANATION OF FIGURES

14 A to F represent various stages in the interstitial (mesenchymal) cells of the testis during normal development, inanition, and refeeding. All magnified × 630. *A*, normal newborn (Si 1.4). *B*, normal adult (S 14). *C*, underfeeding, three to ten weeks of age (S. 7.32). *D*, extreme atrophy in underfeeding from three to ten weeks of age (S 11.65). *E*, underfeeding from three weeks to 428 days of age (St. 44.4). *F*, refed thirty-seven days after underfeeding from three to ten weeks of age (S. 12.52).



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